

Peggy and Charles

STEPHENSON CANCER CENTER

at The University of Oklahoma

Cancer Research Symposium

Symposium Keynote

Stephen M. Prescott, MD

President, Oklahoma Medical Research Foundation

Cancer Health Disparities Keynote

Russell Glasgow, PhD

Associate Director of the Colorado Health Outcomes Program and

Visiting Professor, Department of Family Medicine

University of Colorado School of Medicine

January 31, 2014 • Oklahoma City

Samis Family Education Center

University of Oklahoma Health Sciences Center

The Peggy and Charles Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Settlement Endowment Trust (TSET) for co-sponsoring the 2014 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 13 Highlights

With support from the Oklahoma TSET Cancer Research Program the Stephenson Cancer Center accomplished the following in FY 13:

- Increased cancer center membership by 17% (130 to 152 members) at seven academic institutions across Oklahoma
- Recruited five new cancer researchers to Oklahoma
- Secured \$20.5 million in total grant funding related to cancer and tobacco prevention and control research
- Funded 13 seed and directed-research grants to cancer investigators in Oklahoma

- Established three new Shared Resource facilities in Cancer Functional Genomics, Cancer Tissue Pathology, and Biostatistics
- Hosted over 30 research seminar speakers
- Hosted an international Tumor Micro Environment Conference
- Hosted its 2nd 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 111 new cancer clinical trials
- Enrolled 1,341 patients to clinical trials related to cancer
- Enrolled 478 patients to cancer therapeutic trials
- Opened 11 new Phase I clinical trials
- Enrolled 116 patients to Phase I clinical trials
- Received a five-year \$10 million Center of Biological Research Excellence (CoBRE) grant from the NIH to mentor promising junior cancer investigators
- Was selected as a Tissue Source Site for the NCI's Cancer Genome Atlas Project
- Implemented initiatives with the Oklahoma Medical Research Foundation and OU Norman to jointly recruit cancer investigators and develop joint Shared Resources to support researchers

The Peggy and Charles Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Research Center (OTRC) for co-sponsoring the 3rd Annual 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.

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. In addition, collaborations also make OTRC experts and infrastructure available to TSET grantees and to OSDH tobacco-related programs and staff, thereby increasing the potential national and international scientific impact of their state-based activities.

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

Contact Information:

Oklahoma Tobacco Research Center
Stephenson Cancer Center
800 NE 10th Street, Room 5037
Oklahoma City, OK 73104
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Schedule & Agenda

Cancer Research Symposium Schedule at a Glance

7:30 - 8:15 a.m.	Registration, Continental Breakfast and Poster Set Up
8:15 - 8:25 a.m.	Welcome Address
8:25 - 9:00 a.m.	Symposium Keynote Address When Will We Cure Cancer(s)? From Bedside to Bench and Back Stephen Prescott, MD
9:00 - 9:10 a.m.	Break
9:10 - 10:10 a.m.	Concurrent Session I
10:10 - 10:30 a.m.	Break
10:30 - 11:30 a.m.	Concurrent Session II
11:30 - 1:30 p.m.	Lunch and Poster Viewing
1:30 - 2:30 p.m.	Concurrent Session III
2:30 - 2:40 p.m.	Break
2:40 - 3:40 p.m.	Concurrent Session IV
3:40 - 4:00 p.m.	Break
4:00 - 5:00 p.m.	Concurrent Session V 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)

9:10-10:10 a.m. CONCURRENT SESSION I

B / T / C	TUMOR CELL BIOLOGY AND METASTASIS Session Chair: Ralf Janknecht, PhD	Level Two Auditorium
9:10-9:30	EPIGENETIC SILENCING OF ARRDC3 EXPRESSION IN BASAL-LIKE BREAST CANCER CELLS Jun Chung, PhD Department of Physiology University of Oklahoma Health Sciences Center	
9:30-9:50	EPSIN PROMOTES BREAST CANCER PROGRESSION AND METASTASIS BY CONTROLLING NF-κB ACTIVATION Hong Chen, PhD Cardiovascular Biology Program Oklahoma Medical Research Foundation	
9:50-10:10	EXTRACELLULAR MATRIX TOPOGRAPHY AND GEOMETRIC CUES DIRECT DIFFERENT PATTERNS OF GLIOBLASTOMA MIGRATION James Battiste, MD, PhD Department of Neurology University of Oklahoma Health Sciences Center	
CHD	CANCER HEALTH DISPARITIES TRACK KEYNOTE ADDRESS	Level B B3
9:10-10:10	IMPLEMENTATION SCIENCE: LESSONS LEARNED INTERVENING IN COMPLEX, LOW-RESOURCE SETTINGS Russell Glasgow, PhD Associate Director of the Colorado Health Outcomes Program and Visiting Professor, Department of Family Medicine University of Colorado School of Medicine	

10:30-11:30 a.m. CONCURRENT SESSION II

B / T / C	DRUG DISCOVERY Session Chair: Xin Zhang, MD, PhD	Level Two Auditorium
10:30-10:50	REGULATION OF THE CELL CYCLE BY METFORMIN IS P21-DEPENDENT IN LUNG CANCER Amanda Templeton Department of Pathology University of Oklahoma Health Sciences Center	
10:50-11:10	IDENTIFICATION AND CHARACTERIZATION OF A POTENT FLT3 INHIBITOR Yun Chen Department of Pathology University of Oklahoma Health Sciences Center	
11:10-11:30	EFFECTS OF OKN-007 IN A F98 GLIOMA MODEL ASSESSED BY 1H MR SPECTROSCOPY Patricia Coutinho de Souza, DVM, MSc Advanced Magnetic Resonance Center Oklahoma Medical Research Foundation	
CHD	CANCER HEALTH DISPARITIES PANEL Session Chair: James Mold, MD	Level B B3
10:30-11:30	PANEL: SUCCESS AND FAILURE IN IMPLEMENTATION SCIENCE HELPING PROGRAMS IMPROVE THEIR CHANCES OF WORKING IN “REAL-WORLD” SETTINGS Russell Glasgow, PhD Associate Director of the Colorado Health Outcomes Program and Visiting Professor, Department of Family Medicine University of Colorado School of Medicine James Mold, MD, MPH Professor and Director of Research Division Department of Family and Preventive Medicine University of Oklahoma Health Sciences Center David Bard, PhD Associate Professor, Department of Pediatrics University of Oklahoma Health Sciences Center	

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

B / T / C	THERAPEUTIC RESISTANCE Session Chair: Joe Zhao, PhD	Level Two Auditorium
1:30-1:50	INTERLEUKIN-8/CXCR2 MEDIATES RESISTANCE TO ANTI-VEGF THERAPY IN OVARIAN CANCER Sukyung Woo, PhD Department of Pharmaceutical Sciences University of Oklahoma Health Sciences Center	
1:50-2:10	DOWNREGULATION OF HuR AS A NOVEL MECHANISM OF RADIOSENSITIZING TRIPLE NEGATIVE BREAST CANCER CELLS Anupama Munshi, PhD Department of Radiation Oncology University of Oklahoma Health Sciences Center	
2:10-2:30	NUCLEOSIDE TRANSPORT AND CANCER THERAPY Franklin A. Hays, PhD Department of Biochemistry and Molecular Biology University of Oklahoma Health Sciences Center	
CHD	ENDING THE TOBACCO EPIDEMIC: WHERE WE'VE BEEN AND WHERE WE'RE GOING Session Chair: Ted Wagener, PhD	Level B B3
1:30-1:45	FIFTY YEARS OF PROGRESS IN TOBACCO CONTROL Tracey Strader, MSW Executive Director, Oklahoma Tobacco Settlement Endowment Trust	
1:45-2:00	E-CIGARETTE USE AMONG CURRENT AND RECENT FORMER SMOKERS Ashley White, MPH Department of Biostatistics and Epidemiology University of Oklahoma Health Sciences Center	
2:00-2:15	AN EXAMINATION OF CURRENT AND PAST TOBACCO USE IN COLLEGE STUDENTS IN A TIME OF RAPIDLY EVOLVING TOBACCO PRODUCTS Ellen Meier, MS Department of Psychology Oklahoma State University Oklahoma Tobacco Research Center	
2:15-2:30	Q&A Session	

2:40-3:40 p.m. CONCURRENT SESSION IV

B / T / C	TARGET IDENTIFICATION	Level Two Auditorium
2:40-3:00	RECONSTITUTION OF R-SPONDIN:LGR4:ZNRF3 ADULT STEMCELL GROWTH FACTOR SIGNALING COMPLEXES WITH RECOMBINANT PROTEINS PRODUCED IN <i>ESCHERICHIA COLI</i> Augen Pioszak, PhD Department of Biochemistry and Molecular Biology University of Oklahoma Health Sciences Center	
3:00-3:20	ZEBRAFISH MODELS OF HUMAN T CELL LEUKEMIA AND LYMPHOMA J. Kimble Frazer, MD, PhD Jimmy Everest Section of Pediatric Hematology and Oncology Department of Pediatrics University of Oklahoma Health Sciences Center	
3:20-3:40	G α_{i2} INTERACTION WITH Src AND β -pix IN INVADOPODIA ACTIVATES Rac IN A p130Cas-DEPENDENT MANNER THAT STIMULATES OVARIAN CANCER CELL MIGRATION AND INVASION Jeremy Ward, PhD Department of Cell Biology University of Oklahoma Health Sciences Center	
CHD	KNOWLEDGE GENERATION AND INTERVENTIONS TO ADDRESS DISPARITIES IN CANCER CONTROL	Level B B3
2:40-2:50	ANALYSIS OF IMPACT OF DISTANCE FROM RESIDENCE TO TREATMENT CENTER ON THE OUTCOME OF PATIENTS WITH ACUTE MYELOID LEUKEMIA David Lam, MD Section of Hematology and Oncology Department of Internal Medicine University of Oklahoma Health Sciences Center	
2:50-3:00	THE PROSPECTIVE ASSOCIATION OF YOUTH ASSETS WITH TOBACCO USE IN YOUNG ADULTS Marshall Cheney, PhD Department of Health and Exercise Science University of Oklahoma	

3:00-3:10 BEHAVIORAL RISK FACTORS AMONG CANCER SURVIVORS IN OKLAHOMA

Dana Mowls, MPH
Department of Biostatistics & Epidemiology
College of Public Health
University of Oklahoma Health Sciences Center

3:10-3:20 CANCER IN THE WORKPLACE: HEALTH CARE EXPENDITURES, HOSPITALIZATIONS, AND PRODUCTIVITY LOSSES WITHIN U.S. EMPLOYER SETTINGS

Grant Skrepnek, PhD
Department of Pharmacy: Clinical and Administrative Sciences
University of Oklahoma Health Sciences Center

3:20-3:40 Q&A Session

4:00-5:00 p.m. CONCURRENT SESSION V

B / T / C

NOVEL METHODOLOGIES

Session Chair: Priyabrata Mukherjee, PhD

Level Two
Auditorium

4:00-4:20 THE WARBURG EFFECT: MEASUREMENT OF GAS PHASE BIOMARKERS FOR IMPROVED CANCER DETECTION

Patrick J. McCann, PhD
School of Electrical and Computer Engineering
University of Oklahoma

4:20-4:40 COMPARISON OF TEMPERATURE-SENSITIVE LIPOSOMES FOR TRIGGERED DRUG DELIVERY TO TUMOR UNDER MAGNETIC RESONANCE- AND ULTRASOUND GUIDED HIGH INTENSITY FOCUSED ULTRASOUND

Ashish Ranjan, DVSc, PhD
Center for Veterinary Health Sciences
Oklahoma State University

4:40-5:00 A NEW MODEL FOR PREDICTION OF NEAR-TERM BREAST CANCER RISK

Bin Zheng, PhD
School of Electrical and Computer Engineering
University of Oklahoma

CHD

Translational Think Tank:

Using Tele-Oncology to Improve Cancer Care

Session Chair: Mark Doescher, MD, MSPH

Level B
B3

Keynote Speaker Biography

Stephen M. Prescott, MD

President, Oklahoma Medical Research Foundation

An internationally recognized leader in the studies of the basic mechanisms of human disease, Dr. Stephen Prescott comes to OMRF from the University of Utah, where he was a professor of internal medicine and held the H.A. & Edna Benning Presidential Endowed Chair, founded the Eccles Program in Human and Molecular Biology and Genetics, and served as the executive director of the Huntsman Cancer Institute.

At OMRF, Prescott has overseen the largest campus expansion in the foundation's 67-year-history. The centerpiece of this growth is OMRF's new research tower. Completed in 2011, the 186,000-square-foot tower has earned gold-level LEED certification and, crowned by 18 wind turbines, is believed to house the world's largest rooftop wind farm. To date, Prescott has raised \$85 million to fund OMRF's expansion, which includes not only the new tower but also the addition of more than a dozen new principal scientists to OMRF's faculty. Under Prescott's leadership, the National Institutes of Health has designated OMRF as one of only seven Autoimmunity Centers of Excellence in the U.S., and OMRF has earned seven consecutive four-star ratings—the highest possible score—from Charity Navigator, the nation's leading nonprofit evaluator. During this time, *The Scientist* magazine has also twice named OMRF among its "Best Places to Work" in academia.

A native of Texas, Dr. Prescott received his undergraduate degree at Texas A&M University and his M.D. degree from the Baylor College of Medicine. He has authored more than 250 scientific articles, served as a senior editor of the influential *Journal of Biological Chemistry* and is on the board of the *Journal of Clinical Investigation*. He has also served on medical and scientific advisory committees for the National Institutes of Health, the American Heart Association, and the American Cancer Society. He is a founder of LineaGen, a biotechnology company. Among the awards he has received are the Utah Governor's Medal for Science and Technology, the Sol Sherry Prize from the American Heart Association, and the Houssay-Braun-Menendez Medal from the Argentine Association for the Advancement of Science.

**Concurrent Sessions:
Information
&
Abstracts**

Concurrent Session I – Basic / Translational / Clinical

9:10 a.m. – 10:10 a.m.

Level Two, Auditorium

Tumor Cell Biology and Metastasis

Session Chair: Ralf Janknecht, PhD

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|------------------------|---|
| 9:10 a.m. – 9:30 a.m. | EPIGENETIC SILENCING OF ARRDC3 EXPRESSION IN BASAL-LIKE BREAST CANCER CELLS
Jun Chung, PhD
Department of Physiology
University of Oklahoma Health Sciences Center |
| 9:30 a.m. – 9:50 a.m. | EPSIN PROMOTES BREAST CANCER PROGRESSION AND METASTASIS BY CONTROLLING NF- κ B ACTIVATION
Hong Chen, PhD
Cardiovascular Biology Program
Oklahoma Medical Research Foundation |
| 9:50 a.m. – 10:10 a.m. | EXTRACELLULAR MATRIX TOPOGRAPHY AND GEOMETRIC CUES DIRECT DIFFERENT PATTERNS OF GLIOBLASTOMA MIGRATION
James Battiste, MD, PhD
Department of Neurology
University of Oklahoma Health Sciences Center |

EPIGENETIC SILENCING OF ARRDC3 EXPRESSION IN BASAL-LIKE BREAST CANCER CELLS

Presenter: Jun Chung, PhD

Younghwa Soung¹, Kevin Pruitt², and Jun Chung¹

¹Department of Physiology and Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, ²Department of Molecular and Cellular Physiology, Louisiana State University Health Science Center

Arrestin domain-containing 3 (ARRDC3) is a tumor suppressor molecule that links E3 ligase to phosphorylated substrates such as β -adrenergic receptor and integrin α 4 so that it induces the faster turnover of these activated receptors. Recent studies reveals that expression of ARRDC3 is either lost or suppressed in basal-like breast cancer (BLBC). However, the mechanism by which BLBC suppresses ARRDC3 expression is not established. Here, we show that expression of ARRDC3 in BLBC cells is suppressed at the transcriptional level. Suppression of ARRDC3 expression in BLBC cells involves epigenetic silencing as inhibitors of class III histone deacetylases (HDACs) significantly restores ARRDC3 levels in BLBC cells. SIRT2, among class III HDACs, plays a major role in epigenetic silencing of ARRDC3 in MDA-MB-231 cells. Acetylation levels of the ARRDC3 promoter in BLBC cells is significantly lower than that of other sub-types of BC cells. Chromatin immunoprecipitation analysis established SIRT2 binding at ARRDC3 promoter in BLBC cells. Our studies indicate that SIRT2 dependent epigenetic silencing of ARRDC3 is one of the important events that may contribute to the aggressive nature of BLBC cells.

This work is supported by National Institute of Health (1R01CA163657-01A1).

EPSIN PROMOTES BREAST CANCER PROGRESSION AND METASTASIS BY CONTROLLING NF- κ B ACTIVATION

Presenter: Hong Chen, PhD

Xiaofeng Cai, Satish Pasula, Yong Wei, Yunzhou Dong, Kandice L. Tessneer, Kai Song, Scott Hahn, John McManus, Xiaolei Liu, Baojun Chang, Lili Yu, Yiyuan Chen, Lijun Xia, Yibin Kang, and Hong Chen

Cardiovascular Biology Program, Oklahoma Medical Research Foundation

Epsins are a family of endocytic clathrin adaptors. We have previously reported that epsin deficiency inhibits tumor growth by disrupting angiogenic signaling balance in vascular endothelial cells. However, the pattern of tumor-intrinsic expression of epsin and its influence on cancer growth and metastasis is still unclear. Here, we demonstrate that epsin is upregulated in human cancers, including breast cancer, where its high expression correlates with poor relapse-free survival. Epsin promotes cell proliferation and invasion *in vitro*, and breast tumorigenesis and metastasis *in vivo*. Mechanistically, epsin interacts with and stabilizes TNFR1 signaling complex in breast cancer cells and enhances NF- κ B signaling. Our findings suggest an important role of epsin in contributing to breast cancer progression and metastasis.

EXTRACELLULAR MATRIX TOPOGRAPHY AND GEOMETRIC CUES DIRECT DIFFERENT PATTERNS OF GLIOBLASTOMA MIGRATION

Presenter: James D. Battiste, MD, PhD

James D. Battiste, Bruce Mickey, Young-tae Kim, Tomoyuki Mashimo, Brian Mickey, Cheng-jen Chuong, Digant Dave, Robert M. Bachoo

Introduction: Diffuse single cell infiltration into surrounding normal brain is a pathological hallmark of glioblastoma. 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.

Methods: To investigate the role of extracellular matrix topography in glioblastoma migration we developed an *in vitro* microfluidic platform in which a defined, 3D extracellular matrix geometry was micro-patterned to form channels of varying diameters (20, 15, 10, 8 & 5 μm) approximating the confinement of cells in the brain. CD133+ 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 ability of the cells to migrate was challenged by either antibodies targeting the cell surface or chemicals aimed at disrupting cell migration.

Results: On channels larger than the cell diameter, i.e. 10-20 μm wide, on coated laminin lanes, tumor cells assumed a spindle shaped morphology and migrated. In these channels, glioblastoma cells were seen to extend broad processes (similar to lamellipodia) which provide traction for forward motion (mesenchymal pattern), and this mode of migration was inhibited by an antibody to beta-1 integrin. As the cells entered into more confined 3-D segments (8 μm and 5 μm), there was a mechanical deformation of the nucleus, and the tumor cells assumed an amoeboid morphology with intense active 'blebbing' at leading and trailing edges. Amoeboid pattern of migration was blocked by blebbistatin and ROCK-1 inhibitor but not the beta-1 integrin antibody.

Conclusion: This data suggests that glioblastoma cells are able to migrate using only three dimensional confinement as a source 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. This microfluidic chamber can now serve as a platform for further characterization of migration mechanisms of glioma cells and as a platform to screen new therapies to stop cell migration.

Concurrent Session I – Cancer Health Disparities

9:10 a.m. – 10:10 a.m.

Level B, Room B3

Keynote Address:

IMPLEMENTATION SCIENCE: LESSONS LEARNED

INTERVENING IN COMPLEX, LOW-RESOURCE SETTINGS

Russell Glasgow, PhD

Associate Director, Colorado Health Outcomes Program and Visiting Professor, Department of Family Medicine, University of Colorado School of Medicine, and Former Deputy Director for Implementation Science, National Cancer Institute

Dr. Glasgow's address will review what implementation science is, the needs it addresses, how it is similar to and different from other types of science, and opportunities for research in this area. He will recap the significant developments in the field of implementation science and its relevance for cancer control and prevention in the context of low resource contexts. Although many intervention efforts have been developed in response to cancer health disparities, there has been inadequate translation of these efforts into real-world clinical and public health practice settings and aimed at populations with disproportionate health risks.

The learning objectives for his talk include the following:

1. Summarize key findings in the emerging field of implementation science
2. Articulate the need for multi-level perspectives, contextual information, adaptation to local settings, and a health equity focus in implementation and dissemination projects.
3. Define and provide examples of the key dimensions of the RE-AIM framework and how it is relevant to health disparities
4. Enumerate potential funding and research opportunities to both advance implementation science and address health disparities

Russell Glasgow, PhD

Associate Director of the Colorado Health Outcomes Program and
Visiting Professor, Department of Family Medicine,
University of Colorado School of Medicine
Former Deputy Director for Implementation Science, National Cancer Institute

Dr. Russell Glasgow is recognized nationally and internationally as an expert in the field of dissemination and implementation science, having been the primary developer of RE-AIM - one of the most widely recognized models (<http://cancercontrol.cancer.gov/IS/reaim/>). Most recently, he was Deputy Director for Implementation Science in the Division of Cancer Control and Population Science at the U. S. National Cancer Institute, and he has been responsible for guiding some of NCI's flagship research dissemination tools such as Cancer Control P.L.A.N.E.T., the Cancer Trends Progress Report, and State Cancer Profiles.

Dr. Glasgow is a behavioral scientist specializing in the design and evaluation of practical and generalizable behavior change interventions in health care, worksite, and community settings. He has worked on many transdisciplinary research questions including worksite health promotion, primary care based interventions, and community-based prevention programs involving community health centers and Native American tribes. He has researched target behaviors ranging from smoking prevention and cessation to chronic illness management, patient-provider communication, use of interactive technologies in health care, quality improvement and guidelines adherence. He has published over 400 scientific articles and received the Society of Behavioral Medicine Award as Outstanding Scientist.

Concurrent Session II – Basic / Translational / Clinical

10:30 a.m. – 11:30 a.m. Level Two, Auditorium

Drug Discovery

Session Chair: Xin Zhang, MD, PhD

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|-------------------------|---|
| 10:30 a.m. – 10:50 a.m. | REGULATION OF THE CELL CYCLE BY METFORMIN IS P21-DEPENDENT IN LUNG CANCER
Amanda Templeton
Department of Pathology
University of Oklahoma Health Sciences Center |
| 10:50 a.m. – 11:10 a.m. | IDENTIFICATION AND CHARACTERIZATION OF A POTENT FLT3 INHIBITOR
Yun Chen
Department of Pathology
University of Oklahoma Health Sciences Center |
| 11:10 a.m. – 11:30 a.m. | EFFECTS OF OKN-007 IN A F98 GLIOMA MODEL ASSESSED BY 1H MR SPECTROSCOPY
Patricia Coutinho de Souza, DVM, MSc
Advanced Magnetic Resonance Center
Oklahoma Medical Research Foundation |

REGULATION OF THE CELL CYCLE BY METFORMIN IS P21-DEPENDENT IN LUNG CANCER

Presenter: Amanda K. Templeton

Amanda K Templeton^{1,2}, Qi Wang^{1,2}, and Rajagopal Ramesh^{1,2,3}

¹ Department of Pathology, ² Peggy and Charles Stephenson Cancer Center, ³ The Graduate Program in Biomedical Sciences, University of Oklahoma Health Sciences Center

The oral antidiabetic agent metformin has antineoplastic activity that is likely mediated by mechanisms independent of its hypoglycemic effects. Previously reported in human non-small cell lung carcinoma (NSCLC) cell lines, 24 h treatment with metformin induced growth inhibition and G0/G1 phase arrest through induction of the energy sensing kinase AMP-activated kinase (AMPK) and the DNA damage responsive protein ataxia telangectasia mutated (ATM). AMPK and ATM are both known to regulate G0/G1 and G2 phases through modulation of the p53-p21 axis. Therefore, the objective of our study was to elucidate the molecular mechanism of metformin induced cell cycle arrest in NSCLC. Congruent with previous findings, we demonstrate that 5mM metformin treatment for up to 72 h inhibits growth in H1299 and A549 NSCLC cell lines, but not in the non-cancerous fibroblast cell line MRC-9. In H1299 and A549 cells, growth inhibition was associated with an induction of phosphorylation of AMPK and ATM as well as a reduction in phosphorylation of AKT and mTOR. Extending these findings using H1299 cells, metformin consistently induced only a transient G0/G1 phase arrest at 24 h by downregulating cyclin D1 and p27 and upregulating p21 and at 72 h a G2/M-arrest by accumulating cyclin B1 and upregulating p21 and p27. These arrests were associated with ATM and Chk-2 activation and resultant inhibitory phosphorylation of cyclin dependent phosphatase CDC25c. Importantly, p21 knock down in H1299 cells demonstrated the coordinate loss of p27 stabilization, attenuation of the G0/G1 phase arrest at 24 h, and decrease in inhibitory phosphorylation of pan-cyclin dependent kinases. Therefore, we demonstrate for the first time in NSCLC that metformin activates G1 and G2 -checkpoint responses, but the fidelity of the G1-arrest is compromised by the downregulation of p27. However, p21-dependent upregulation of p27 facilitates a G2/M arrest at 72 h. The ability of metformin to control aberrant oncogenic cell-cycle regulation by inducing negative cell-cycle regulators p21 and p27 may provide a novel therapeutic strategy in lung cancer.

IDENTIFICATION AND CHARACTERIZATION OF A POTENT FLT3 INHIBITOR

Presenter: Yun Chen

Yun Chen, Yao Guo, Wanting Ho and Zhizhuang Joe Zhao

Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Acute myeloid leukemia (AML) is a malignant myeloid disorder for which there is no effective treatment. Gain-of-function mutations of tyrosine kinase FLT3 are frequently found in AML patients. This makes FLT3 an attractive therapeutic target. Currently, several potent FLT3 inhibitors have been developed. However, their clinical efficacy is limited largely due to their poor effectiveness toward the FLT3-D835 mutants which are often present in AML or acquired after treatment of FLT3-ITD-positive AML with tyrosine kinase inhibitors. Needless to say, more potent FLT3 inhibitors targeting both FLT-ITD and FLT3-D835 mutants are needed. In addition, combinations of tyrosine kinase inhibitors with drugs targeting other signaling pathways represent a new trend in anti-cancer drug development.

To establish an effective kinase assay for FLT3 inhibitor screening, we generated a protein substrate designated GST-FLT3S which was expressed in *E. coli* cells as a glutathione S-transferase fusion protein. The protein substrate together with recombinant proteins containing the catalytic domain of wild type and mutant forms of FLT3 expressed in baculovirus was used in biochemical screening of inhibitors. Several potent inhibitors were obtained. Importantly, one of the inhibitors with an oxindole core structure inhibited FLT3 and D835 FLT3 mutants equally well with nanomolar IC₅₀ values. We further analyzed the potency of the inhibitor by performing cell-based assays. The cells used included FLT3-ITD-positive cell line MV-4-11 and an EPO-dependent erythroleukemia cell line transformed by retrovirus mediated expressions of FLT3-ITD and FLT3-D835 mutants. At nanomolar concentrations, the inhibitor blocked growth factor signaling and effectively caused apoptosis and cell cycle arrest. It showed significant advantage over the current available FLT3 inhibitor, sorafenib.

Loss-of-function mutations of tumor suppressor p53 are common in solid tumors but relatively rare in AML although its expression is often suppressed. This makes p53 a potential target for anti-AML drug development. We employed MDM2 inhibitor nutlin-3 which blocks the degradation of p53. Importantly, at sub-nanomolar concentrations, FLT3 inhibitors and nutlin-3 synergistically inhibited growth of cells containing FLT3-ITD or FLT3-D835 mutants.

Altogether, we developed an effective substrate for screening of FLT3 inhibitors and identified one compound with high potency toward both FLT3-ITD and FLT3-D835. We further demonstrated that targeting FLT3 and p53 simultaneously greatly increases drug potency.

EFFECTS OF OKN-007 IN A F98 GLIOMA MODEL ASSESSED BY 1H MR SPECTROSCOPY

Presenter: Patricia Coutinho de Souza, DVM, MSc

Patricia Coutinho de Souza¹, Krithika Balasubramanian¹, Nataliya Smith¹, Debra Saunders¹, Changho Choi², Rheal A Towner¹

¹Advanced Magnetic Resonance Center, Oklahoma Medical Research Foundation, Oklahoma City, OK, ²Advanced Imaging Research Center, Univ. of Texas Southwestern Medical Center, Dallas, TX

Gliomas are the most frequent form of adult primary brain tumors. OKN-007 (2,4-disulfophenyl-PBN) is a nitron that has demonstrated anti-glioma effects in several rodent models and is currently a clinical investigational drug for recurrent gliomas. Magnetic resonance spectroscopy (MRS) provides metabolite/biochemical information about tissues *in vivo*. In this study, we evaluated the anti-tumor effects of OKN-007 in a F98 rat glioma model by assessing metabolite alterations with MRS. The metabolites that were quantitatively measured were: total creatine (tCr), total choline (tCho), N-acetyl aspartate (NAA), and total lipids at 5.3ppm, 1.3 ppm, and 0.9 ppm.

The peak areas of all metabolites were normalized to the area of tCr. There was a significant decrease in the Cho/Cr ($p=0.0003$), NAA/Cr ($p=0.0396$), Lip5.3/Cr, ($p<0.0001$), Lip1.3/Cr ($p<0.0001$), Lip0.9/Cr ($p<0.0001$) ratios, in OKN-007 treated gliomas compared to untreated gliomas.

The results of this study demonstrate that OKN-007 could affect tumor metabolism, which was denoted by significant changes in concentration of different lipids in the F98 glioma model following treatment. We are currently working on the assessment of cell death (apoptosis and necrosis), cell density, and proliferative index for both untreated and OKN-007 treated groups, and these results will be evaluated in association with our MRS data.

Concurrent Session II – Cancer Health Disparities

10:30 a.m. – 11:30 a.m.

Level B, Room B3

Implementation Science Panel

SUCCESS AND FAILURE IN IMPLEMENTATION SCIENCE

Helping programs improve their chances of working in “real-world” settings

The goal for this session is to provide a forum for the exchange of experiences and ideas related to the application of implementation science in cancer prevention and control. In addition to Dr. Russell Glasgow, who is providing the keynote address on implementation science for the CHD Track of the symposium, panelists include two OUHSC faculty members who have a depth of experience in studying the implementation of evidence-based practices (EBPs).

Each of the panelists will briefly share their implementation science backgrounds after which they will throw the floor open to discussion of real world cases. Several researchers and practitioners will come prepared to describe cases and problem-solve solutions, but all participants are invited to join in the discussion and share from their own experiences. At the conclusion the panelists will summarize the themes common to the cancer prevention and control cases discussed and offer suggestions for advancing IS research in Oklahoma. James Mold will serve as panel facilitator.

Panelists:

Russell Glasgow, PhD, Visiting Professor, Department of Family Medicine and Associate Director, Colorado Health Outcomes Program, University of Colorado School of Medicine

James Mold, MD, MPH, Professor and Director of Research Division, Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center

David Bard, PhD, Associate Professor, Department of Pediatrics, University of Oklahoma Health Sciences Center

Russell Glasgow, PhD

Dr. Glasgow is Associate Director of the Colorado Health Outcomes Program and Visiting Professor, Department of Family Medicine at the University of Colorado School of Medicine. He is a recognized nationally and internationally as an expert in the field of dissemination and implementation science, having been the primary developer of RE-AIM - one of the most widely recognized models (<http://cancercontrol.cancer.gov/IS/reaim/>). Most recently, he was Deputy Director for Implementation Science in the Division of Cancer Control and Population Science at the U. S. National Cancer Institute, and he has been responsible for guiding some of NCI's flagship research dissemination tools such as Cancer Control P.L.A.N.E.T., the Cancer Trends Progress Report, and State Cancer Profiles.

Dr. Glasgow is a behavioral scientist specializing in the design and evaluation of practical and generalizable behavior change interventions in health care, worksite, and community settings. He has worked on many transdisciplinary research questions including worksite health promotion, primary care based interventions, and community-based prevention programs involving community health centers and Native American tribes. He has researched target behaviors ranging from smoking prevention and cessation to chronic illness management, patient-provider communication, use of interactive technologies in health care, quality improvement and guidelines adherence. He has published over 400 scientific articles and received the Society of Behavioral Medicine Award as Outstanding Scientist.

James Mold, MD

Dr. Mold is a tenured Professor and Director of the Research Division in the Department of Family and Preventive Medicine at the University of Oklahoma Health Sciences Center in Oklahoma City. Educated at the University of Michigan, Duke University School of Medicine, and the OU College of Public Health, and raised in North Carolina, he left private practice to join the OUHSC faculty in 1984.

Dr. Mold is the founder and Research Director of the Oklahoma Physicians Resource/Research Network (OKPRN), a large and very successful regional primary care practice-based research network involving primary care clinicians and practices throughout Oklahoma. He adapted the practice facilitator concept originated in England and uses facilitators to assist clinicians in research and quality improvement projects. In collaboration with Oklahoma clinicians, he has pioneered approaches to the re-engineering of primary care practices to facilitate the delivery of evidence-based services more effectively and economically.

His novel ideas and research methods have merited national attention and funding from a very wide variety of funders (e.g., the National Institutes of Health, the Agency for Healthcare Research and Quality, and the Robert Wood Johnson Foundation, etc.), and many other practice-based research networks have adopted his innovations. He is the author or co-author of more than 120 peer-reviewed journal articles and was elected to the Institute of Medicine of the National Academies of Science in 2008. In 2012, he was awarded the George Lynn Cross Research Professorship by David Boren, President of the University of Oklahoma. Most recently, Dr. Mold and his colleagues have developed the conceptual basis for a primary health care extension system, similar to Cooperative Extension in agriculture, through which innovations can be more efficiently disseminated, implemented, and diffused, and gaps between the public health, mental health, and private practice systems can be narrowed. As a result of an AHRQ grant called IMPaCT (Infrastructure for Maintaining Primary Care Transformation), he is actively developing this model in Oklahoma, Arkansas, Missouri, and Colorado at the present time.

David Bard, PhD

Dr. Bard is a health services researcher with expertise in methodology, biostatistics, psychometrics, informatics, genetics, and behavioral science. He is currently Associate Professor of Pediatrics and Director of the Biomedical and Behavioral Methodology Core at the University of Oklahoma Health Sciences Center. His research interests include clinical and field trials methodology, testing and measurement in the behavioral sciences, behavior genetics, and applied science in the area of Adverse Childhood Experiences.

Dr. Bard is active in two ongoing programs of health services research. As a member of the Center on Child Abuse and Neglect, Dr. Bard is highly active in research evaluating the efficacy and effectiveness of interventions aimed at prevention of future child maltreatment and general improvement of family and child health and well-being. Much of this work has centered on rigorous outcomes research and the implementation science (i.e., uptake of research findings in routine healthcare settings) of maternal and infant early childhood home visitation (MIECHV) programs. As a second line of health services research, Dr. Bard is also actively studying various early childhood developmental disorders. This work is focused on the epidemiology of attention deficit/hyperactivity disorder (ADHD), autism spectrum disorders, and conduct and oppositional defiant disorders as well as the efficacy and effectiveness of front-line treatments for these disorders.

Dr. Bard is currently the principal investigator for two large external evaluations of maternal and infant health home-based programs throughout the state of Oklahoma and of early care and education opportunities for children in or at-risk of entering foster-care. He is the Co-PI for a state-funded evaluation of early education and assessment services for children with autism, and investigator on four on-going field implementation studies involving maltreatment prevention programs and community-based treatment and education programs for children with developmental delays.

Concurrent Session III – Basic / Translational / Clinical

1:30 p.m. – 2:30 p.m. Level Two, Auditorium

Therapeutic Resistance

Session Chair: Joe Zhao, PhD

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|-----------------------|--|
| 1:30 p.m. – 1:50 p.m. | <p>INTERLEUKIN-8/CXCR2 MEDIATES RESISTANCE TO ANTI-VEGF THERAPY IN OVARIAN CANCER
Sukyung Woo, PhD
Department of Pharmaceutical Sciences
University of Oklahoma Health Sciences Center</p> |
| 1:50 p.m. – 2:10 p.m. | <p>DOWNREGULATION OF HuR AS A NOVEL MECHANISM OF RADIOSENSITIZING TRIPLE NEGATIVE BREAST CANCER CELLS
Anupama Munshi, PhD
Department of Radiation Oncology
University of Oklahoma Health Sciences Center</p> |
| 2:10 p.m. – 2:30 p.m. | <p>NUCLEOSIDE TRANSPORT AND CANCER THERAPY
Franklin A. Hays, PhD
Department of Biochemistry and Molecular Biology
University of Oklahoma Health Sciences Center</p> |

INTERLEUKIN-8/CXCR2 MEDIATES RESISTANCE TO ANTI-VEGF THERAPY IN OVARIAN CANCER

Presenter: Sukyung Woo, PhD

Bharat Devapatla, Ankur Sharma, and Sukyung Woo

Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center

Purpose: Vascular endothelial growth factor (VEGF) families of ligands and receptors are primary signaling pathways in tumor angiogenesis and have been extensively targeted by cancer therapeutics. Ovarian tumors are highly vascularized and high degrees of tumor angiogenesis and VEGF expression in ovarian carcinomas correlate with poorer survival. Encouraging results have been obtained with trials in ovarian cancer that target the VEGF and its receptor. However, the clinical benefits are short-lived, followed by a restoration of tumor progression. Understanding the mechanisms of tumor escape from anti-VEGF therapy is critical to find strategies to overcome the resistance. The purpose of this study was to investigate the potential targets of ovarian cancer resistance to anti-VEGF treatments using experimental phenotypic resistance models.

Methods: We generated SKOV3 ovarian cancer xenograft in athymic nude mice and treated with sorafenib (10 mg/kg daily, PO) or bevacizumab (10 mg/kg BIW, IP) over an 8-week period. Treatment-resistance tumors were defined by a long-term trend toward continued tumor progression (> 50% increase from the initial volume) under bevacizumab or sorafenib treatment after an initial response whereas treatment-sensitive tumors were defined by a long-term trend toward stable disease or regression. We performed mouse and human angiogenesis multiplex assay to identify the soluble factor differences in the plasma of resistant and sensitive mice. To examine the role of IL-8 mediated resistance, we disrupted IL-8 function of SKOV3 and HUVEC using pharmacological inhibitors (e.g., anti-IL-8 antibody or IL-8 receptor CXCR2 inhibitor) for in vitro assays of cell growth inhibition, spheroid formation, and cell migration. Further, we evaluated the effectiveness of sorafenib and SB 225002 combination in vivo in SKOV3 xenograft mice. CXCR2 expression was evaluated in human ovarian cancer tissue micro array (TMA).

Results: In both sorafenib and bevacizumab resistant mice, IL-8 levels were elevated by 2 to 4 folds compared to their respective sensitive treatment groups in a time-dependent manner. Growth inhibition was significantly higher in SKOV3 (32%, $P = 0.002$) and HUVEC (25%, $P = 0.015$) cells when treated with a CXCR2 inhibitor SB 225002 (2 μ M) and sorafenib (4 μ M) compared to sorafenib alone. SB 225002 (2 μ M) disrupted the spheroid formation in SKOV3 cells. SB 225002 and sorafenib combination treatment resulted in 40% less migration of SKOV3 cells when compared to treatment with sorafenib alone.

Conclusion: Our results suggest that IL-8 may serve as an important target for sorafenib and bevacizumab resistance in ovarian cancer and disruption of IL-8 activity via CXCR2 inhibition could improve outcomes of anti-VEGF therapy.

Downregulation of HuR as a novel mechanism of radiosensitizing triple negative breast cancer cells

Presenter: Anupama Munshi, PhD

Kanthesh M Basalingappa^{1,3}, Meghna Mehta^{1,3}, James N Griffith^{1,3}, Ranganayaki Muralidharan^{2,3}, Myriam Gorospe⁴, Rajagopal Ramesh^{2,3}, and Anupama Munshi^{1,3}
Departments of ¹Radiation Oncology, ²Pathology and ³Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK., ⁴Laboratory of Genetics, National Institute on Aging, National Institutes of Health, Baltimore, MD.

HuR is a ubiquitously expressed member of the Elav/Hu family of RNA-binding proteins which can associate with mRNAs containing AU-rich elements in their 3'-untranslated regions. It is predominantly a nuclear protein that translocates to the cytoplasm in response to stress signals and stabilizes mRNAs encoding proteins implicated in cell proliferation, angiogenesis, apoptosis, and stress response. Studies examining HuR expression in human cancers indicated that elevated cytoplasmic HuR expression is associated with a high histologic grade, large tumor size, and poor survival of patients with cancer, leading to the hypothesis that cytoplasmic HuR abundance could be a prognostic marker in cancer patients. It has been reported that altering the subcellular distribution of HuR leads to a decrease in mRNA stability and increases tamoxifen responsiveness in breast cancer cells. As the role of HuR in radiation resistance has not been previously evaluated, we designed this study to determine the role of HuR in mediating radiation response of human breast cancer cells. Subcellular fractionation studies in a panel of breast cancer cells [triple negative (MDA-MB-231, MDA-MB-468 and Hs578t), luminal (MCF-7), and normal mammary epithelial (MCF-10a)] demonstrated elevated cytoplasmic levels of HuR in the more aggressive triple negative breast cancer cells (TNBC) compared to the normal mammary and the luminal cells. TNBCs also had high expression of HuR mRNA and total protein as observed by quantitative (Q) RT-PCR and western blot analysis. To test if high expression of HuR contributed to the radiation resistance of TNBCs, HuR was silenced and cells were exposed to various doses of radiation. Clonogenic assays indicated that silencing HuR enhanced tumor cell radiosensitivity in MDA-MB-231, MDA-MB-468 and Hs578t cells, with the survival fraction at 2Gy declining from 59%, 49%, 65% in control (scrambled siRNA-transfected cells) to 40%, 33%, 46% in HuR-silenced cells, respectively. MCF-7 and MCF-10a cells were not radiosensitized upon HuR silencing. Since HuR plays a central role in cancer it is possible that multiple pathways and mechanisms are affected by HuR knockdown and could contribute to the observed radiosensitivity. Molecular studies suggested that HuR silencing in combination with radiation modulated the expression of several genes involved in cell survival, cell cycle and DNA repair in MDA-MB-231 cells. The involvement of the DNA repair pathway following treatment with siHuR was assessed using γ -H2AX foci as a marker. Our results show that a higher number of radiation-induced γ -H2AX foci are present in HuR-silenced MDA-MB-231 cells compared with control cells, suggesting that suppression of the double-strand DNA repair pathway. The persistence of γ -H2AX foci was not seen in the MCF-7 cells. We propose that HuR knockdown enhances the radioresponse of TNBC cells by inhibiting the repair of radiation-induced double-strand DNA breaks.

Grant support: This work was supported by the NIH Grant Number 1P20GM103639-01 from the COBRE Program of the National Institutes of Health.

NUCLEOSIDE TRANSPORT AND CANCER THERAPY

Presenter: Franklin A. Hays, PhD

Rebba C. Boswell-Casteel, Jennifer M. Johnson, Kelli D. Duggan, and Franklin A. Hays
Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences
Center, Stephenson Cancer Center

Equilibrative nucleoside transporters (ENTs) are polytopic integral membrane proteins that have been shown to modulate the efficacy of chemotherapeutics by serving as cellular gatekeepers for nucleoside-derived drug absorption. Nucleoside analogs, such as gemcitabine, are dependent on ENTs for entrance into eukaryotic cells. Higher ENT expression levels, the absence of ENT mutations, and homologous ENT expression profiles have been strongly correlated to increased survival in gemcitabine-treated pancreatic cancer patients. Unfortunately, little is known about the molecular basis of substrate transport. There is currently no available structural data or functional assays using purified protein to aid in functional analysis. Our current studies are focused on developing functional assays for purified ENTs as a foundation for defining the molecular mechanism of substrate selectivity and transport to aid in targeted drug design.

Function Unknown Now 26 (FUN26) is a yeast ortholog of the human ENT family. FUN26 was expressed, purified to homogeneity, and incorporated into proteoliposomes for functional analysis. Our results demonstrate that FUN26 is: 1) functional in a purified form using a defined proteoliposome system, 2) has broad selectivity for nucleosides and nucleobases, 3) has high affinity for uridine and cytidine nucleosides, 4) preferentially transports pyrimidines over purines, and 4) is sensitive to changes in the 2' and 5' position of nucleoside substrates. This study provides the first demonstration of functional activity of a purified eukaryotic ENT.

Concurrent Session III – Cancer Health Disparities

1:30 p.m. – 2:30 p.m.

Level B, Room B3

Research Presentations

ENDING THE TOBACCO EPIDEMIC

Where we've been and where we're going

Fifty years have passed since the 1964 Surgeon General's report on smoking and health. Since that time, the prevalence of smoking has declined by more than half with the help of clinical and public health interventions, as well as strategic and effective public policy. Unfortunately, smoking continues to be the leading preventable cause of premature disease and death in the United States. In this session, we will present not only the steps taken over the last 50 years to achieve such significant reductions in tobacco use but will also discuss next steps and new challenges, such as emerging tobacco products, involved in ending the tobacco epidemic once and for all.

Session Chair:

Theodore Wagener, PhD, TSET Tobacco Research Scholar, Stephenson Cancer Center and Oklahoma Tobacco Research Center, and Assistant Professor, Department of Pediatrics, University of Oklahoma Health Sciences Center

Presenters:

Tracey Strader, MSW

FIFTY YEARS OF PROGRESS IN TOBACCO CONTROL

Ashley White, MPH

E-CIGARETTE USE AMONG CURRENT AND RECENT FORMER SMOKERS

Ellen Meier, MS

AN EXAMINATION OF CURRENT AND PAST TOBACCO USE IN COLLEGE STUDENTS IN A TIME OF RAPIDLY EVOLVING TOBACCO PRODUCTS

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.

FIFTY YEARS OF PROGRESS IN TOBACCO CONTROL

Presenter: Tracey Strader, MSW

Tracey Strader

Executive Director, Oklahoma Tobacco Settlement Endowment Trust

Significant strides have been made since the Surgeon General's report in 1964 calling attention to the devastating health effects of smoking. Increased consumer awareness of the negative health effects of smoking, smoke-free policies, tobacco taxation, mass media campaigns, marketing restrictions, and public and clinical health interventions have all contributed to the 25% decline in smoking prevalence. Over the last 50 years, however, we have also witnessed 20 million smoking-related deaths, a slowing in the reduction of smoking prevalence, and smoking remains the single largest cause of preventable death and disease in the United States. To continue and in fact accelerate the demise of tobacco-related harm, proven and effective tobacco control policies must be continued and strengthened in order to meet the upcoming challenges of ending the tobacco epidemic.

E-CIGARETTE USE AMONG CURRENT AND RECENT FORMER SMOKERS

Presenter: Ashley White, MPH

Ashley H. White, Laura A. Beebe, Alayna P. Tackett, Theodore L. Wagener, Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center

The use of electronic cigarette/vapor devices (ECVD) is gaining popularity in the state of Oklahoma. We are interested in determining if smokers and recent former smokers (RFS) in Oklahoma are using ECVD and, if so, the preferred types of devices and the reasons for their use.

We analyzed cross-sectional data from the Oklahoma Behavioral Risk Factor Surveillance System (BRFSS) for January-June 2013. Current smokers (n=338) and RFS (n=59) were asked about use of ECVD in places where smoking is not allowed and which cessation strategies were used during their most recent quit attempt. Preliminary data indicates that many smokers use ECVD as a substitute for smoking. Thirty-five percent of current smokers and 47% of RFS said they had used an ECVD in a place where smoking was not allowed. Switching to an ECVD as a method of smoking cessation during the last successful quit or quit attempt was reported by 25% of RFS, surpassing other methods such as telephone quitlines (7%), switching to other smokeless tobacco products (5%), or using current FDA approved cessation methods, such as the nicotine patch (10%) and pharmacotherapy (10%). Women (31%) were more likely than men (18%) to report switching to an ECVD to help them quit but less likely to report using a more traditional cessation product. Respondents aged 18-38 were more likely than any other age group to report switching to an ECVD for the purpose of quitting smoking (37%). Fifty-nine percent of smokers and RFS said they had used an ECVD where they couldn't smoke but had not switched in order to quit combustible cigarettes, indicating dual use.

These findings suggest that a significant proportion of current smokers in Oklahoma may be using ECVD as a supplemental nicotine method in smoking ban locations and alternatively, to help quit the use of combustible cigarettes. These findings also suggest that women and younger adults are most likely to switch to ECVD for the purpose of quitting combustible cigarettes. While the present findings shed light on the current use of ECVD, more research is needed to better assess and understand these behaviors.

AN EXAMINATION OF CURRENT AND PAST TOBACCO USE IN COLLEGE STUDENTS IN A TIME OF RAPIDLY EVOLVING TOBACCO PRODUCTS

Presenter: Ellen Meier

Ellen Meier^{1,3}, M.S., Alayna P. Tackett^{1,3}, B.A., Mary Beth Miller¹, M.S., DeMond M. Grant^{1,3}, Ph.D., Theodore L. Wagener^{2,3}, Ph.D.

¹Oklahoma State University, Department of Psychology

²University of Oklahoma Health Sciences Center, Department of Pediatrics

³Oklahoma Tobacco Research Center

Background: Concerns have been raised regarding emerging tobacco products (ETPs), such as, e-cigarettes and snus and their potential effects on youth tobacco use; specifically, whether they may become a gateway product for further tobacco use. Similarly, use of Hookah or waterpipe tobacco, a long-standing tobacco product world-wide, appears to be increasing among U.S. college students. Because most smokers begin smoking in adolescence, it is important to understand how trying certain products can affect one's risk for future use.

Purpose: The present study aims to determine the prevalence of various tobacco products among youth on a college campus and whether the first product tried predicts subsequent regular, dual, or poly tobacco use.

Method: Undergraduate students ($N = 1304$) at a large university southern plains university completed an online survey of past/current use of cigarettes, smokeless tobacco (SLT), hookah, ETPs (i.e., dissolvables, snus, e-cigarettes), and nicotine replacement therapy (NRT). Students were further classified as single, dual, or polytobacco users.

Results: The sample consisted of 79.5% non-users, 13.8% single, 4.4% dual, and 1.5% poly users. Overall, 49.4% of participants reported trying a tobacco product. Hookah was the most tried product (38%), but cigarettes were most often the first product ever tried (51%). First product tried did not discriminate between current tobacco use and non-use, but individuals who first tried SLT or cigarettes (rather than hookah or ETPs) were more likely to be poly-users of tobacco. Current tobacco users who first tried ETPs or hookah were largely non-daily users of hookah; current tobacco users who first tried cigarettes or SLT were largely non-daily or daily users of cigarettes and/or SLT.

Conclusions: Hookah and ETPs are increasingly becoming the first tobacco product ever tried by youth; however, the uptake of ETPs is poor and, unlike cigarettes and SLT, does not appear to lead to significant daily/non-daily use of cigarettes and SLT. Continued surveillance of use of ETPs, especially e-cigarettes and hookah, is vital, as these products will continue to proliferate. As such, their potential as gateway products will likely only continue to increase.

Concurrent Session IV – Basic / Translational / Clinical

2:40 p.m. – 3:40 p.m.

Level Two, Auditorium

Target Identification

Session Chair: Lawrence Rothblum, PhD

2:40 p.m. – 3:00 p.m.

RECONSTITUTION OF R-SPONDIN:LGR4:ZNRF3 ADULT STEMCELL GROWTH FACTOR SIGNALING COMPLEXES WITH RECOMBINANT PROTEINS PRODUCED IN *ESCHERICHIA COLI*

Augen Pioszak, PhD

Department of Biochemistry and Molecular Biology

University of Oklahoma Health Sciences Center

3:00 p.m. – 3:20 p.m.

ZEBRAFISH MODELS OF HUMAN T CELL LEUKEMIA AND LYMPHOMA

J. Kimble Frazer, MD, PhD

Jimmy Everest Section of Pediatric Hematology and Oncology

Department of Pediatrics

University of Oklahoma Health Sciences Center

3:20 p.m. – 3:40 p.m.

$G\alpha_{i2}$ INTERACTION WITH SRC AND β -pix IN INVADOPODIA ACTIVATES RAC IN A p130Cas-DEPENDENT MANNER THAT STIMULATES OVARIAN CANCER CELL MIGRATION AND INVASION

Jeremy Ward, PhD

Department of Cell Biology

University of Oklahoma Health Sciences Center

RECONSTITUTION OF R-SPONDIN:LGR4:ZNRF3 ADULT STEM CELL GROWTH FACTOR SIGNALING COMPLEXES WITH RECOMBINANT PROTEINS PRODUCED IN ESCHERICHIA COLI

Presenter: Augen A. Pioszak, PhD

Heather E. Moad and Augen A. Pioszak

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

R-spondins are secreted glycoproteins (RSPO1-RSPO4) that have proliferative effects on adult stem cells by potentiating Wnt signaling. Aberrant RSPO signaling is implicated in various cancers. RSPO actions are mediated by the leucine-rich repeat (LRR)-containing 7-transmembrane receptors LGR4-LGR6 and the transmembrane E3 ubiquitin ligases ZNRF3 and RNF43, which are tumor suppressors. Here, we present a methodology for bacterial expression and purification of the signaling competent, cysteine-rich Fu1-Fu2 domains of the four human RSPOs, a fragment of the human LGR4 extracellular domain (ECD) containing LRR1-14, and the human ZNRF3 ECD. In a cell-based signaling assay the nonglycosylated RSPOs enhanced low-dose Wnt3a signaling with potencies comparable to those of mammalian cell-produced RSPOs and RSPO2 and -3 were more potent than RSPO1 and -4. LGR4 LRR1-14 and ZNRF3 ECD inhibited RSPO2-enhanced Wnt3a signaling. The RSPOs bound LGR4 LRR1-14 with nanomolar affinities that decreased in the following order in a TR-FRET assay: RSPO4 > RSPO2 > RSPO3 > RSPO1. RSPO-receptor interactions were further characterized with a native gel electrophoretic mobility shift assay, which corroborated the RSPO-LGR4 TR-FRET results and indicated that RSPOs weakly bound ZNRF3 with affinities that decreased in the following order: RSPO2 > RSPO3 > RSPO1. RSPO4:ZNRF3 complexes were not detected. Lastly, ternary RSPO:LGR4:ZNRF3 complexes were detected for RSPO2 and -3. Our results indicate that RSPO and LGR4 N-glycans are dispensable for function, demonstrate RSPO-mediated ternary complex formation, and suggest that RSPO signaling potency is determined by the ability of the RSPO to form the ternary complex. Our unique protein production methodology may provide a cost-effective source of recombinant RSPOs for regenerative medicine applications.

This work was supported by a grant from the Oklahoma Center for Adult Stem Cell Research (OCASCR).

ZEBRAFISH MODELS OF HUMAN T CELL LEUKEMIA AND LYMPHOMA

Presenter: J. Kimble Frazer MD, PhD

Lance Batchelor MS, Stephanie Schatzman-Bone, Julie Hawkins, Ryuichiro Kimura PhD, Barbara Squiban PhD, J. Kimble Frazer MD, PhD

Jimmy Everest Section of Pediatric Hematology and Oncology, Department of Pediatrics, University of Oklahoma Health Sciences Center

Leukemias and lymphomas are the 1st and 3rd most common cancers of childhood, representing nearly 50% of all pediatric oncology diagnoses. T cell acute lymphoblastic leukemia (T-ALL) and T cell lymphoblastic lymphoma (T-LBL) are common subtypes of these diseases. The genetic origins and molecular mechanisms driving these two closely-related cancers are poorly understood, which limits the development of new targeted therapies. To discover the genetic pathways that promote T cell oncogenesis and identify new therapeutic targets, we employ novel approaches using a vertebrate model organism: zebrafish (*Danio rerio*).

Zebrafish are well-suited to oncology research, particularly studies of hematologic cancers. *D. rerio* possess both innate and adaptive immune systems, a spleen, thymus, and hematopoietic marrow, and B, T, and NK cells. Consequently, like humans, they can develop lymphoid malignancies. We created three zebrafish lines with unique heritable germline mutations that predispose them to T-ALL and T-LBL. Using these mutant lines, we have investigated the genomic and gene expression changes that drive vertebrate T cell cancers, and identified new proto-oncogene, tumor suppressor, and tumor progressor candidates. In addition, we have used zebrafish with T cell cancers to test new anti-neoplastic compounds *in vivo*, to determine their therapeutic efficacy. An overview of our laboratory's research program will be presented.

G α_{i2} INTERACTION WITH SRC AND β -PIX IN INVADOPODIA ACTIVATES RAC IN A P130CAS-DEPENDENT MANNER THAT STIMULATES OVARIAN CANCER CELL MIGRATION AND INVASION

Presenter: Jeremy D. Ward, PhD

Jeremy D. Ward^{1,2,3} and Danny N. Dhanasekaran^{1,2}

¹Stephenson Cancer Center, University of Oklahoma Health Sciences Center; ²Department of Cell Biology, University of Oklahoma Health Sciences Center; ³College of Medicine, University of Oklahoma Health Sciences Center

Although the role of G proteins and their receptors in the pathobiology of cancer is being increasingly realized, their precise role in tumorigenesis and tumor progression is not fully understood. To this end, our study demonstrates that the G protein G α_{i2} plays a very active role in promoting cell migration and invasion by its localization to invadopodia in ovarian cancer cells. In this report, we demonstrate that lysophosphatidic acid (LPA) signaling causes the translocation of G α_{i2} into the invadopodia leading to its interaction with the tyrosine kinase Src and the guanine nucleotide exchange factor β -pix. We also demonstrate that G α_{i2} , through a p130Cas-dependent pathway, activates Rac1 in ovarian cancer cells. Importantly, this study is the first to demonstrate the functional interaction of β -pix with G α_{i2} and to show that this interaction occurs in the invadopodia. Moreover, our report reveals that knockdown of G α_{i2} in the context of LPA signaling leads to loss of β -pix and active Rac association in the invadopodia and leads to a significant decrease in the overall activation of Rac in these cells. Finally, we show that knockdown of G α_{i2} leads to the complete loss of translocation to p130Cas to focal adhesions and that the total distribution of Src was shifted primarily from invadopodia to the perinuclear region, indicating that Src is inactivate when G α_{i2} is knocked down. Overall, our current study dramatically adds to the current understanding of how the G protein G α_{i2} contributes to the migration and invasion of ovarian cancer cells and is suggestive that other G proteins may play analogous roles. Consequently, our report provides tantalizing evidence that G α_{i2} may be a critical signaling component of a large signaling complex in the invadopodia that if disrupted could serve as an excellent target for therapy in ovarian and potentially other cancers.

Concurrent Session IV – Cancer Health Disparities

2:40 p.m. – 3:40 p.m.

Level B, Room B3

Research Presentations

KNOWLEDGE GENERATION AND INTERVENTIONS TO ADDRESS DISPARITIES IN CANCER CONTROL

This theme-related session will feature emerging research being conducted by investigators on questions related to cancer prevention and control or cancer health disparities. The Cancer Health Disparities Program of the Stephenson Cancer Center is dedicated to fostering the generation of high quality cancer prevention and control research, which addresses cancer health disparities and is responsive to the needs of tribal and other high-risk, underserved communities in Oklahoma. Information on faculty membership, public seminars, and other activities of the Cancer Health Disparities Program will be available following this session.

Session Chair:

Mark Doescher, MD, MSPH, Program Leader, Cancer Health Disparities Program, Stephenson Cancer Center, and Professor of Family Medicine, University of Oklahoma Health Sciences Center

Presenters:

David Lam, MD

ANALYSIS OF IMPACT OF DISTANCE FROM RESIDENCE TO TREATMENT CENTER ON THE
OUTCOME OF PATIENTS WITH ACUTE MYELOID LEUKEMIA

Marshall Cheney, PhD

THE PROSPECTIVE ASSOCIATION OF YOUTH ASSETS WITH TOBACCO USE IN YOUNG ADULTS

Dana S. Mowls, MPH

BEHAVIORAL RISK FACTORS AMONG CANCER SURVIVORS IN OKLAHOMA

Grant H. Skrepnek, PhD

CANCER IN THE WORKPLACE: HEALTH CARE EXPENDITURES, HOSPITALIZATIONS, AND
PRODUCTIVITY LOSSES WITHIN U.S. EMPLOYER SETTINGS

Mark Doescher, MD, MSPH

Mark Doescher is the Leader of the Cancer Health Disparities (CHD) research program at the Charles and Peggy 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 population. Current activities include the development of a prevention research that promotes physical activity and healthy eating; reduces tobacco use; and increases the uptake of recommended cancer screenings. The CHD program is also developing a program of research to improve the quality of cancer care delivery in rural and tribal communities. System-level interventions to enhance cancer care coordination between oncologists and primary care providers are being developed, as are interventions to establish tele-oncology outreach between the Peggy and Charles Stephenson Cancer Center and tribal health care systems.

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 also leads 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 a member of the Journal of Rural Health editorial board.

ANALYSIS OF IMPACT OF DISTANCE FROM RESIDENCE TO TREATMENT CENTER ON THE OUTCOME OF PATIENTS WITH ACUTE MYELOID LEUKEMIA

Presenter: David Lam, MD

David Lam, MD¹, Hossein Maymani, MD², Michael G Machiorlatti, MS³, Samer A Srour, MB ChB⁴, Minh Phan, MD², George Selby, MD¹, Jennifer L. Holter-Chakrabarty, MD¹, and Mohamad Cherry, MD¹

¹Section of Hematology and Oncology, College of Medicine, University of Oklahoma Health Sciences Center; ²Department of Internal Medicine, University of Oklahoma Health Sciences Center; ³Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center; ⁴Marrow and Stem Cell Transplant Program, University of Oklahoma Health Sciences Center

Introduction: Acute myeloid leukemia (AML) is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemia in the United States. Limited data is available comparing epidemiology and treatment according to the distance from patient residence to treatment center. Oklahoma University Health Sciences Center (OUHSC) is the major tertiary center for Oklahoma residents to receive treatment for AML. We utilize a retrospective analysis of adults with AML treated at our institution evaluating the impact on distance from center with treatment outcomes of survival, remission, and relapse.

Methods: From January 2000 until June 2011 we identified a total of 269 patients with 216 meeting inclusion criteria for the study with the diagnosis of AML. To evaluate the relationship between overall survival and distance a Kaplan-Meier (with a log rank test) and a Cox proportional hazard model evaluating covariates of interest were performed. A logistical regression was performed to assess association of all covariates with relapse and complete remission.

Results: Distance of residence to OUHSC of 50-75 miles and 75-100 miles (compared to >100 miles) indicates an increased hazard of death with hazard ratio of 2.61 ($p = 0.0014$) and 1.83 ($p=0.0481$) after adjusting for age. Patients living closer to OUHSC (0-25 miles & 25-50 miles) as compared to areas further from OUHSC (>100 miles) do not have a significantly greater hazard of death. There are differences in the survival curves for the five different distance groups (Figure 2; $p=0.0040$). The predicted probability of complete remission is lower in patients 50-75 miles from OUHSC (OR =0.317; $p= 0.0386$) as compared to patients living >100 miles away adjusting for age and risk type. Other distance groups did not demonstrate statistical significance for complete remission.

Conclusions: Patients living 0-50 and over 100 miles have a similar hazard of death, which could be explained by proximity to OUHSC or outlying tertiary care centers, with most being located over 100 miles from OUHSC. The increase in hazard of death in patients living 50-100 miles from OUHSC may be attributed to increased distance to a tertiary care center that provide varying levels of supportive care for leukemic patients should complications arise post discharge. There is evidence of a significant decrease in the probability of achieving a complete remission in patients living 50-75 miles from OUHSC as compared to those living >100 miles. However, since these patients received similar induction regimens, further analysis will be conducted to determine a cause for this finding.

THE PROSPECTIVE ASSOCIATION OF YOUTH ASSETS WITH TOBACCO USE IN YOUNG ADULTS

Presenter: Marshall Cheney, PhD

Marshall Cheney, PhD¹; Roy Oman, PhD²; and Sara Vesely, PhD³

¹Department of Health and Exercise Science, University of Oklahoma, ²Department of Health Promotion Sciences, College of Public Health, University of Oklahoma Health Sciences Center,

³Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center

Developmental assets protect adolescents from tobacco use, but their influence during the transition to young adulthood is unknown. Prospective analyses were conducted using five waves of annual data collected from 487 randomly-selected ethnically-diverse youth (baseline age = 15 to 17) participating in the Youth Asset Study. Logistic regression, controlling for age, family structure, parent education, and ethnicity, was conducted to prospectively examine associations between ten assets assessed at wave 1 with tobacco use in the last 30 days at wave 5. Six family-related assets (Family Communication, Relationship with Mother, Relationship with Father, Parental Monitoring, Non-Parental Adult Relationship, and Positive Peer Role Model) and four individual assets (General Self-Confidence, Future Educational Aspirations, General Future Aspirations, and Responsible Choices) were examined. Six wave 1 assets were significantly associated with tobacco use in the last 30 days at wave 5. Youth without the Relationship with Father (OR 2.25), Positive Peer Role Model (OR 2.46), General Aspirations for the Future (OR 2.48), and Responsible Choices (OR 1.91) assets at wave 1 had odds of reporting tobacco use at wave 5 that were two times greater than those with the asset. There was a significant interaction between family structure and two assets. Youth in two-parent families without the Non-Parental Adult Relationship asset (OR 2.94) had odds of reporting tobacco use at wave 5 three times greater than those with the asset. Youth in 2-parent families without the Future Educational Aspirations asset (OR 2.69) had higher odds of reporting wave 5 tobacco use than those who had the asset. These data show that developmental assets were significantly associated with reduced odds of tobacco use 4 years later. These results suggest that interventions focusing on developmental assets in older adolescents still benefit youth as they transition to young adulthood and can protect against tobacco use in young adulthood. Interventions focusing on developing or maintaining positive relationships with parents and other adults may be especially beneficial to young adults.

Table 1 Prospective Association of Youth Assets at Wave 1 with Tobacco Use in the Last 30 Days at Wave 5	
Asset	wave 1 asset, wave 5 tobacco use
Family Communication	OR 1.36 (0.91, 2.01)
Relationship with Mother	OR 1.24 (0.76, 2.03)
Relationship with Father	OR 2.25 (1.40, 3.62)
Parental Monitoring	OR 1.61 (0.84, 3.09)
Non-Parental Adult Relationship	Interaction
Positive Peer Role Model	OR 2.46 (1.63, 3.70)
General Self-Confidence	OR 1.08 (0.65, 1.79)
Future Educational Aspirations	Interaction
General Future Aspirations	OR 2.48 (1.33, 4.61)
Responsible Choices	OR 1.91 (1.08, 3.39)

BEHAVIORAL RISK FACTORS AMONG CANCER SURVIVORS IN OKLAHOMA

Presenter: Dana S. Mowls, MPH

Dana S. Mowls, MPH and Laura A. Beebe, PhD

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

Disparities exist in cancer morbidity and mortality, which likely stem from behaviors such as smoking and lack of physical activity. The purpose of this research was to examine the prevalence of lifestyle behaviors that may impact survivorship and quality of life among adult cancer survivors in the state of Oklahoma.

Cross-sectional data were derived from 2011 and 2012 Oklahoma Behavior Risk Factor Surveillance System. Respondents were asked questions assessing cancer diagnosis and were identified as either having had cancer, not including skin, (n=1,256) or no prior cancer (n=13,724). Weighted prevalence estimates and 95% confidence intervals (CI) were computed for covariates of interest by cancer diagnosis. Gender differences were explored. Covariates examined were cigarette smoking (current, former, never), heavy alcohol consumption (>1 beverage per day for females, >2 beverages per day for males), any physical activity in past 30 days (yes, no), body mass index (underweight, normal, overweight, obese), total daily fruit consumption, total daily vegetable consumption, perceived poor mental health days in the past month (0, 1-15, 16-30) and perceived poor physical health days in the past month (0, 1-15, 16-30).

Overall, 5.4% (CI: 5.0-5.8) of respondents had been diagnosed with cancer. The prevalence of current smoking was similar among those with (25.8%, CI: 22.3-29.2) and without (25.2%, CI: 22.3-29.2) cancer. Although heavy alcohol consumption was slightly lower among those with (3.7%, CI: 2.2-5.3) as compared to without (5.2%, CI: 4.6-5.7) cancer, this was not significantly different. The prevalence of no physical activity was significantly higher among those with cancer (41.9%, CI: 38.3-45.6) as compared to without (28.5%, CI: 27.5-29.5) cancer. Obesity was not found to be different among those with (31.5%, CI: 28.0-34.9) and without (31.8%, CI: 30.8-33.0) cancer. The prevalence of 16 to 30 days of poor physical health among respondents with cancer (23.6%, CI: 20.4-26.8) was more than twice that among respondents without cancer (9.4%, CI: 8.8-10.0).

Despite being diagnosed with cancer, cancer survivors report high prevalences of unhealthy behaviors. Approximately one in four cancer survivors are current smokers, one in five does not engage in physical activity, and one in three is reported to be obese. Cancer survivors are now living longer making it imperative to reduce unhealthy lifestyle behaviors that may increase the risk of re-occurrence and worsen their quality of life.

CANCER IN THE WORKPLACE: HEALTH CARE EXPENDITURES, HOSPITALIZATIONS, AND PRODUCTIVITY LOSSES WITHIN U.S. EMPLOYER SETTINGS[†]

Presenter: Grant H. Skrepnek, PhD

Grant H. Skrepnek, Ph.D

College of Pharmacy, University of Oklahoma Health Sciences Center

Objective: To assess outcomes of health care expenditures, hospitalizations, and productivity among employed persons with cancer in the United States from 2004 to 2008.

Methods: Agency for Healthcare Research and Quality's Medical Expenditure Panel Survey data were used in this retrospective cross-sectional study of employed adults aged 18 years or older with any diagnosis of malignant neoplasms. Multivariate regression analyses assessed the study's outcomes according to prominent cancer types and other factors.

Results: Overall, 3.31 million employed persons had cancer annually, incurring productivity losses of approximately 33.4 million disability days. Women's cancers and melanoma were associated with higher burdens of illness relative to other forms.

Conclusions: This nationally representative investigation found that disability days in employed persons with cancer equate to 20% of health care expenditures. Resources present within small organizational settings may be especially important to consider when implementing programs to prevent and cure cancer.

[†] Published as: Tang DH, Alberts DS, Nevins R, Sullivan S, Skrepnek GH. Health Care Expenditures, Hospitalizations, and Productivity Associated With Cancer in US Employer Settings. *Journal of Environmental and Occupational Medicine* 2012; 15(12): 1453-1460. Work completed at The University of Arizona Cancer Center & Center for Health Outcomes and PharmacoEconomic Research, Tucson, AZ.

Concurrent Session V – Basic / Translational / Clinical

4:00 p.m. – 5:00 p.m. Level Two, Auditorium

Novel Methodologies

Session Chair: Priyabrata Mukherjee, PhD

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|-----------------------|--|
| 4:00 p.m. – 4:20 p.m. | THE WARBURG EFFECT: MEASUREMENT OF GAS PHASE BIOMARKERS FOR IMPROVED CANCER DETECTION
Patrick J. McCann, PhD
School of Electrical and Computer Engineering
University of Oklahoma |
| 4:20 p.m. – 4:40 p.m. | COMPARISON OF TEMPERATURE-SENSITIVE LIPOSOMES FOR TRIGGERED DRUG DELIVERY TO TUMOR UNDER MAGNETIC RESONANCE- AND ULTRASOUND GUIDED HIGH INTENSITY FOCUSED ULTRASOUND
Ashish Ranjan, DVSc, PhD
Center for Veterinary Health Sciences
Oklahoma State University |
| 4:40 p.m. – 5:00 p.m. | A NEW MODEL FOR PREDICTION OF NEAR-TERM BREAST CANCER RISK
Bin Zheng, PhD
School of Electrical and Computer Engineering
University of Oklahoma |

THE WARBURG EFFECT: MEASUREMENT OF GAS PHASE BIOMARKERS FOR IMPROVED CANCER DETECTION

Presenter: Patrick J. McCann, PhD

Patrick J. McCann

School of Electrical and Computer Engineering, University of Oklahoma, Norman, OK

Otto Warburg et al. published a paper titled “The Metabolism of Tumors in the Body” in 1927. By measuring the concentrations of glucose and lactic acid in arteries and veins of experimental animals (rats) with and without abdominal tumors the authors concluded that tumor growth was accompanied by a fermentation process rather than solely by a normal respiration process. Today this is known as the Warburg effect. It is the basis for positron emission tomography (PET scan) diagnosis of cancer patients where an isotopically-labeled glucose analog is administered to the patient and regions of high fermentation activity are imaged. It is also the basis for bench instruments, such as Seahorse Bioscience’s XF-96 analyzer, designed to measure oxygen consumption rate (OCR) and extracellular acidification rate (ECAR). OCR and ECAR measurements, which assess mitochondrial respiration and glycolysis rates, respectively, can determine if Warburg effect conditions are present in *in vitro* samples.

A reasonable question to ask is this: Are there any other aspects of the Warburg effect that can be measured? For example, are there small molecule byproducts of the altered metabolic process that have sufficiently high vapor pressure to be exhaled from the lungs? If so, then it should be possible to measure these molecules in exhaled breath and correlate their concentrations to disease conditions. Further research in this area can potentially lead to a better understanding of cancer as well as improved cancer detection and better cancer therapy monitoring. This presentation will review what is currently known about the Warburg effect and provide possible avenues to pursue that will facilitate research efforts in this area. Critical to this work will be the ability to measure easily a variety of suspected Warburg effect metabolites in exhaled breath samples. This presentation will conclude with an update on ongoing work involving the fabrication of novel mid-infrared laser spectrometers, devices that have a proven track record of sensitive real-time detection of specific molecules in exhaled breath.

COMPARISON OF TEMPERATURE-SENSITIVE LIPOSOMES FOR TRIGGERED DRUG DELIVERY TO TUMOR UNDER MAGNETIC RESONANCE- AND ULTRASOUND GUIDED HIGH INTENSITY FOCUSED ULTRASOUND

Presenter: Ashish Ranjan, DVSc, PhD

Ashish Ranjan, Danny Maples, and Venkatesan Perumal
Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK

Solid tumor chemotherapy typically has three major limitations. 1) Insufficient and incomplete drug delivery. Conventional treatment methods cause significant portions of the injected dose to end up in normal organs resulting in severe side effects and limiting the dosage of the therapeutic regime, 2) Presence of dense extracellular matrix and elevated interstitial fluid pressure in tumors resulting in heterogeneous distribution and limited penetration depth (3-5 cell layers from blood vessels), and 3) Absence of reliable methods for real-time control of drug delivery to help guide and localize future interventions. To overcome these limitations and improve reporting of chemotherapeutic distribution in real-time, we have developed a heat-activated imageable low temperature sensitive liposome (LTSL) that permit *in vivo* tracking of liposome distribution under image guidance, and are sensitive to mild, non-destructive HIFU-mediated temperature elevations above normal body temperature (40-42°C). The relative benefits/pitfalls of imageable LTSLs containing a combined payload of gadolinium-based MR contrast agents and Doxorubicin (Dox) with LTSL co-containing Dox along with an echogenic marker for *in vivo* MRI- or Ultrasound-guided HIFU-based tumor drug delivery will be compared and discussed. Data suggests that MR contrast agents can differ substantially from antitumor drugs with respect to rates of intratumoral diffusion and uptake. In contrast, the US-based contrast agents are expected to yield a direct relation between drug distribution and image intensity in a tumor. These novel image-guided targeting concepts can permit us to develop a cost-effective, widely-applicable and –available therapeutic modality providing the unique capability to spatially control safe delivery and distribution of drugs within tumors *in vivo*.

A NEW MODEL FOR PREDICTION OF NEAR-TERM BREAST CANCER RISK

Presenter: Bin Zheng, PhD

Maxine Tan, Yuchen Qiu, Hong Liu, and Bin Zheng,

School of Electrical and Computer Engineering, University of Oklahoma, Norman, OK

We investigated the feasibility of predicting near-term breast cancer risk based on the bilateral mammographic feature asymmetry between the left and right breasts. 994 pairs of negative digital mammograms were retrospectively collected. At next sequential screening examination (12 to 36 months later), 283 women were diagnosed positive for cancer, 349 were recalled but later proved to be benign, and 362 remained negative (not-recalled). From a large pool of 183 image features and 3 clinical features (age, breast density BIRADS, and family cancer history), we applied a Sequential Forward Floating Selection feature selection method to select 10 optimal features and then built a support vector machine (SVM) based risk prediction model, which was tested using a 10-fold cross-validation framework. The area under the ROC curve is 0.73 ± 0.02 for positive and negative/benign case classification. The computed odds ratios demonstrated an increasing risk trend with increasing SVM-generated risk scores (Table 1). This preliminary study demonstrates that bilateral mammographic tissue density asymmetry could be a strong risk factor to predict the risk of women in developing breast cancer in near-term.

Table 1: Adjusted ORs and 95% CIs with increasing SVM-generated risk scores

Subgroup	Positive – Negative/benign Cases	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI)
1	19 – 180	1.00	baseline
2	33 – 166	1.88	[1.03, 3.44]
3	59 – 140	3.99	[2.28, 7.00]
4	60 – 139	4.09	[2.33, 7.17]
5	112 – 86	12.34	[7.12, 21.38]

Concurrent Session V – Cancer Health Disparities

4:00 p.m. – 5:00 p.m.

Level B, Room B3

Translational Think Tank:

Using Tele-Oncology to Improve Cancer Care

This session will engage attendees in a discussion of the challenges and opportunities associated with the delivery of local cancer care services via tele-oncology consultation. After an initial review of the published literature by Mark Doescher and a discussion of the Translational Think Tank format by Dewey Scheid, all session attendees are invited to contribute ideas about how to implement an effective system of tele-oncology care based on their own experience and knowledge.

Triggered by provocative questions, this faculty-facilitated “think tank” dialogue will be an intensive problem-solving discussion focused on identifying people, resources, and a framework for creating tele-oncology services. We expect the audience will include oncologists, primary care physicians, health care administrators, researchers, and others with an interest in this topic. At the think tank’s conclusion, we expected that a small working group will be formed to continue to drive progress in this area -- to include implementation of evidence-based practices and application for funding to evaluate proposed approaches.

Opening by:

Mark Doescher, MD, MSPH, Program Leader, Cancer Health Disparities Program, Stephenson Cancer Center, and Professor of Family Medicine, University of Oklahoma Health Sciences Center

Dewey Scheid, MD, MPH, Professor, Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center

Mark Doescher, MD, MSPH

Mark Doescher is the Leader of the Cancer Health Disparities (CHD) research program at the Peggy and Charles 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 population. Current activities include the development of a prevention research that promotes physical activity and healthy eating; reduces tobacco use; and increases the uptake of recommended cancer screenings. The CHD program is also developing a program of research to improve the quality of cancer care delivery in rural and tribal communities. System-level interventions to enhance cancer care coordination between oncologists and primary care providers are being developed, as are interventions to establish tele-oncology outreach between the Peggy and Charles Stephenson Cancer Center and tribal health care systems.

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 also leads 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 a member of the Journal of Rural Health editorial board.

Dewey Scheid, MD, MPH

Dr. Scheid is a Professor in the Research Division of the Department of Family and Preventive Medicine (DFPM) at the University of Oklahoma Health Sciences Center. His areas of interest include medical decision making and evidence-based medicine. He recently served as Co-Investigator of an AHRQ grant “Using Health Information Technology to Improve Healthcare Quality,” as PI on an AHRQ grant modeling prioritizing of health care for complex patients, and as PI of a long-term study of tobacco cessation supported by a seed grant from the Oklahoma Tobacco Research Center. He has conducted research on colorectal cancer screening funded by the NIH and breast cancer screening funded by Susan G. Komen Foundation. In his work in the DFPM’s Clinical Decision Making Program, he studies ways to support decision-making by health care providers and patients. He is a past recipient of the University Family Medicine Clinic Residency Preceptor of the Year Award.

Currently, as an investigator working on the Community Engagement Key Component Activity of the Oklahoma Shared Clinical and Translational Resource Program (an IDeA-CTR award), Dr. Scheid is developing a Translational Think Tanks Program to bring teams of researchers and community members together to translate specific innovations into practice.

Poster Presentation Abstracts

Cancer Research Symposium Poster Session

11:30 a.m. – 1:30 p.m.

Level 1

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DOUBLECORTIN-LIKE KINASE (DCLK1) SIGNALING IN VIRUS-INDUCED LIVER CANCER Ali, Naushad	41	B/T/C
TUMOR-INFILTRATING LYMPHOCYTE (TIL) GROWTH AS A PROGNOSTIC FACTOR IN PATIENTS (PTS) WITH METASTATIC MELANOMA (MM) Alrwas, Anas	2	B/T/C
AKR1C3 AS A MARKER TO DISTINGUISH WELL DIFFERENTIATED HCC FROM BENIGN HEPATIC LESIONS Annan, Anand C.	3	B/T/C
MANAGEMENT OF INTRACRANIAL MENINGIOMAS USING KEYHOLE AND ENDONASAL TECHNIQUES Archer, Jacob B.	29	B/T/C
VISCEROSENSORY AND LIMBIC NEUROCIRCUITRY UNDERLYING THE HEDONIC EVALUATION OF CIGARETTE CUES Avery, Jason A.	4	B/T/C
BARRIERS AND FACILITATORS OF COLORECTAL CANCER SCREENING BY COLONOSCOPY IN A RURAL NATIVE AMERICAN POPULATION IN OKLAHOMA Baluh, Hope	58	CHD
AG-311 INDUCES RAPID MITOCHONDRIAL DYSFUNCTION IN TRIPLE NEGATIVE BREAST CANCER CELLS Bastian, Anja	30	B/T/C

EXAMINATION OF CANCER PREVENTION AND CONTROL PROGRAMS AT NCI-DESIGNATED CANCER CENTERS Beck, Sarah	59	CHD
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STAKEHOLDER ENGAGEMENT AS A MODEL FOR COMPREHENSIVE TOBACCO POLICY PLANNING IN OKLAHOMA TRIBAL COMMUNITIES Blanchard, Jessica	60	CHD
IMMUNOLOGICALLY MODIFIED CARBON NANOTUBE: A NOVEL STRUCTURE FOR LASER CANCER THERAPY Chen, Wei R.	42	B/T/C
STUDY THE RELATIONSHIP BETWEEN X-RAY ENERGY SPECTRUM BEAM HARDENING AND THE NOISE POWER SPECTRUM IN COMPUTED TOMOGRAPHY (CT) IMAGES Collier, Jason F.	31	B/T/C
LKB1 AS A RAB7 EFFECTOR: IMPLICATIONS FOR THE PRO-ANGIOGENIC RECEPTOR NEUROFILIN-1 Coughlan, Kathleen A.	6	B/T/C
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QUANTIFICATION OF DNA DAMAGE CAUSED BY CIGARETTE SMOKE USING PRIMER-ANCHORED DNA DAMAGE DETECTION ASSAY Ganapathy, Vengatesh	54	CHD
INTERPHASE FLUORESCENCE IN SITU HYBRIDIZATION SIGNAL DETECTION BY COMPUTING INTENSITY VARIANCE ALONG THE OPTICAL AXIS Ghani, Muhammad	32	B/T/C

STUDY THE FEASIBILITY OF RADAITION DOSE OPTIMIZATION IN CT SCANNING PROTOCOLS VIA APPLICATION OF BEAM HARDENING FILTERS Gill, Kamaljit K.	8	B/T/C
SELECTIVE TARGETING AND TREATMENT OF METASTATIC PANCREATIC CANCER VIA THREE FUSION PROTEIN/PRODRUG SYSTEMS Guillen, Katrin P.	33	B/T/C
MICROPTHALMIA TRANSCRIPTION FACTOR (MITF) AS A DIAGNOSTIC MARKER FOR METASTATIC MELANOMAS NEGATIVE FOR OTHER MELANOMA MARKERS WITH FURTHER COMPARATIVE GENOMIC HYBRIDIZATION ANALYSIS Guo, Ruifeng	9	B/T/C
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RECRUITMENT AND RETENTION OF AMERICAN INDIAN SMOKERS INTO A CULTURALLY-TAILORED SMOKING CESSATION STUDY Johnson, Melanie	62	CHD
PREVENTION OF BREAST CANCER LUNG METASTASIS VIA THE BLOCKADE OF THE ADHESION CASCADE Kang, Shin-Ae	12	B/T/C
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RADIATION INSTIGATES EMT, CSC SELF RENEWAL AND PLURIPOTENCY SIGNAL TRANSDUCTION IN NON-TARGETED (BYSTANDER) ERA ⁺ AND TRIPLE-NEGATIVE BREAST CANCER CELLS Khan, Faizan	13	B/T/C
ERLOTINIB IS NOT EFFECTIVE IN PATIENTS (PTS) WITH JAK-2 V617F POSITIVE POLYCYTHEMIA VERA Khawandanah, Mohamad	14	B/T/C
DOWN-REGULATION OF ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP) 1B3 FUNCTION BY PROTEASOME INHIBITOR BORTEZOMIB Khondoker, Alam	36	B/T/C
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EXCISE TAX AND PRICING DIFFERENTIALS AT TRIBAL SMOKE SHOPS IN OKLAHOMA: OPPORTUNITIES FOR HARMONIZATION Laux, Fritz L.	63	CHD
EFFECTS OF DURATION OF ELECTRONIC CIGARETTE USE Lechner, William V.	55	CHD
FORMULATION AND CHARACTERIZATION OF AN ULTRASOUND IMAGEABLE LOW TEMPERATURE SENSITIVE LIPOSOME FOR IMAGE GUIDED DRUG DELIVERY Maples, Danny	38	B/T/C
NECROSIS-INITIATED COMPLEMENT ACTIVATION LEADS TO PROLIFERATION IN MEDULLOBLASTOMA CELLS IN VITRO Maurer, Adrian J.	39	B/T/C
AZD2281, A PARP INHIBITOR, ENHANCES THE RESPONSE OF HUMAN BREAST CANCER CELLS TO IONIZING RADIATION BY SUPPRESSING DNA REPAIR Mehta, Meghna	47	B/T/C
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REGULATION OF OATP1B1 DEGRADATION AND TRAFFICKING VIA UBIQUITIN-PROTEASOME PATHWAY

Presenter: Alaa H. Abuznait

Alaa H. Abuznait, John Powell, Mary Girton, Xiajie Meng, and Wei Yue
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Purpose: Organic anion transporting polypeptide (OATP) 1B1 is a hepatic uptake transport protein that plays an important role in drug disposition. The c. 512T>C (V174A) variant of OATP1B1 (*5) has decreased transport activity *in vitro*, and *in vivo* it is the most robust and important predictor of myopathy induced by OATP1B1 substrate statins. Little is known regarding how function of OATP1B1 is regulated at the post-translational level. The aim of the present study is to elucidate the regulation of OATP1B1 degradation and trafficking by the ubiquitin system.

Method: Stable cell line expressing Flag-tagged OATP1B1*1a was established in HEK293. This stable cell line or HEK293 transiently expressing Flag-tagged OATP1B1*1a or Flag-tagged OATP1B1*5 were treated with proteasome inhibitors (bortezomib and MG132) or vehicle control DMSO for up to 6 hrs. Immunoblot and intracellular accumulation studies using estradiol 17 β -D-glucuronide (E217G, 1 μ M, 3 min) were carried out to investigate the protein levels and functional activity of OATP1B1.

Results: Proteasome activity is efficiently inhibited by bortezomib or MG132 as indicated by increased ubiquitin-conjugated proteins. In HEK293-Flag-tagged OATP1B1*1a cell line, 2 h after treatment, OATP1B1 protein levels increased to 3.9 ± 1.9 and 2.9 ± 1.3 fold for MG132 and bortezomib treatments, respectively, compared to vehicle control treatment. Interestingly, in treatments greater than 2 h, OATP1B1 protein levels gradually decreased to a level similar to control by the 6 h treatment (n=3). Increased amount of higher molecular weight OATP1B1 was observed in both *1a- and *5-transiently transfected HEK293 following proteasome inhibitor treatment, suggesting potential ubiquitination of OATP1B1*1a and *5. The 5 h MG132 treatment decreased OATP1B1*1a-mediated E217G transport by ~30% compared to control.

Conclusions: This is the first indication that protein levels of OATP1B1 are regulated by proteasome inhibition, supporting that the ubiquitin-proteasome pathway is involved in degradation of OATP1B1. Following proteasome inhibition, a compensatory mechanism of OATP1B1 degradation, likely through up-regulation of lysosome degradation, may exist to maintain homeostasis of OATP1B1. This study provides a novel regulatory mechanism of OATP1B1 homeostasis by the anti-cancer drug bortezomib.

DOUBLECORTIN-LIKE KINASE (DCLK1) SIGNALING IN VIRUS-INDUCED LIVER CANCER

Presenter: Naushad Ali, PhD

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Introduction: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. Chronic infections with hepatitis B and C viruses (HBV and HCV respectively) frequently induce hepatic inflammation and cirrhosis. These infections substantially enhance the risk of developing multiple HCC subtypes. The molecular mechanisms of virus-induced fibrosis/cirrhosis and HCC however, are poorly understood. We previously demonstrated that HCV induces multiple putative cancer stem cell (CSC) markers including doublecortin-like kinase (DCLK1), a key regulator of microtubule dynamics. We have further demonstrated that DCLK1 enhances HCV replication, and affects the expression levels of miRNAs and transcription factors that promote solid tumor growth. The molecular mechanisms that regulate signaling pathways involved in promoting hepatocarcinogenesis is largely unknown, and is the fundamental focus of our study.

Methods: Genome-wide transcriptome analysis was carried out using total RNAs isolated from DCLK1-overexpressing and control hepatoma cells. Liver tissue microarrays and specimens representing various stages of liver diseases in patients with chronic hepatitis B or C were analyzed for an array of markers including DCLK1 by immunohistochemical staining and Western blot. Huh7 hepatoma cells were transplanted into the flanks of athymic nude mice to generate HCC-like tumor xenografts. The tumors were analyzed for proteins, mRNAs and miRNAs or treated with siRNA against DCLK1 and scrambled siRNA to monitor tumor growth arrest.

Results: Although normal liver tissues in mice and human lack detectable expression of DCLK1, tumor xenografts of cultured hepatoma cells display clustered, sporadic epithelial and mesenchymal expression patterns. This was accompanied by high-level expression of c-Myc, pro-inflammatory marker S100A9 (MRP14) and activation of NFκB. Genome-wide RNA analysis of HCV-DCLK1 double-positive and HCV-negative hepatoma cells suggests that an array of genes involving cellular metabolism and signaling pathways are affected by DCLK1 overexpression. Examination of liver tissues derived from patients with chronic hepatitis B/C and HCC suggests that DCLK1 and S100A9 proteins are overexpressed in the regenerative nodules, fibrotic septa, mesenchymal cells, endothelium and lymphocytes aggregates. Similar observations were also made in drug-resistance patients. The siRNA-mediated inhibition of DCLK1 caused significant decreased in tumor volume in a xenograft model.

Conclusions: DCLK1 overexpression appears to be intimately related to the activation of pro-inflammatory signals during the development of virus-induced pre-neoplastic conditions and initiation of tumors in liver. Thus, targeting DCLK1 at early stage of liver diseases may prevent virus-induced cirrhosis and HCC.

TUMOR-INFILTRATING LYMPHOCYTE (TIL) GROWTH AS A PROGNOSTIC FACTOR IN PATIENTS (PTS) WITH METASTATIC MELANOMA (MM)

Presenter: A. Alrwas

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Clinical response rates of ~50% have been observed with Adoptive T-cell therapy (ACT) using autologous ex-vivo expanded tumor-infiltrating lymphocytes (TIL) in MM pts. It is possible that pts whose tumors are able to produce TIL may have an improved prognosis that contributes to these results. To test this hypothesis, therapies received and treatment outcomes were collected retrospectively for patients who underwent surgery for TIL harvest at MDACC but who never received TIL therapy. The relationship between successful TIL growth and clinical response rates with other therapies was determined. Successful TIL growth was defined as a yield of $>40 \times 10^6$ TIL cells after 5 weeks culture of tumor fragments in IL-2-containing media, as this criteria is required for treatment with TIL. Among 346 pts, 213 (62%) had successful TIL growth. Pts with successful TIL expansion survived longer from the date of TIL tumor harvest than pts with inadequate TIL growth ($P = 0.01$). Pts with successful TIL growth had significantly higher clinical response rates with chemotherapy ($n = 59$; 14%) compared to pts with insufficient TIL growth ($n = 59$; 0%, $P = 0.006$). Successful TIL growth pts also had a higher response rate to chemotherapy/immunotherapy combinations (CI; $n = 65$; 25%) than non-growers ($n = 57$; 5%, $P = 0.005$). However, no significant correlation was observed for TIL growth status with responsiveness to immunotherapies ($n = 114$, $P = 0.57$) or to BRAF inhibitors (among BRAF-mutant pts; $n = 43$, $P = 0.74$).

In summary, successful TIL growth from resected tumors correlated with improved clinical response rates with chemotherapy and CI, and improved overall survival, but not clinical responsiveness to immune or targeted therapies. These results suggest that TIL growth status may be a prognostic and predictive factor in MM pts.

AKR1C3 AS A MARKER TO DISTINGUISH WELL DIFFERENTIATED HCC FROM BENIGN HEPATIC LESIONS

Presenter: Anand C Annan

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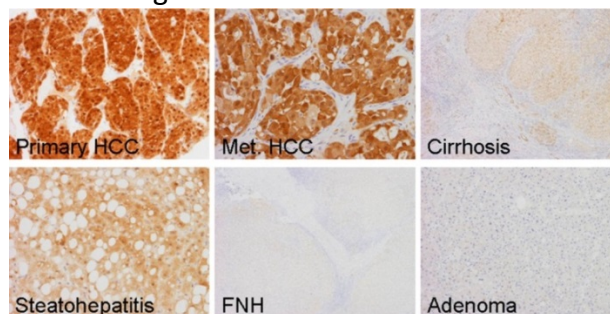
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Background: Aldo-keto reductase family 1 member C3 (AKR1C3) is an enzyme with multiple functions including working as a steroid dehydrogenase. We evaluated the expression of AKR1C3 in hepatitis, hepatic adenoma, cirrhosis, focal nodular hyperplasia (FNH), hepatocellular carcinoma (HCC) and metastatic HCC.

Design: Formalin-fixed, paraffin embedded sections (2 cases of hepatitis, 6 cases of hepatic adenoma, 8 cases of cirrhosis, 6 cases of FNH, 22 cases of HCC, and 3 cases of metastatic HCC) were immunostained for AKR1C3. Immunoreactivities were scored as 0 (no staining), 1+ (focal mild staining), 2+ (diffuse mild/focal strong staining), 3+ (diffuse strong staining). The cases were divided into cohorts of cancer group (HCC and metastatic HCC) and non-cancer group (hepatitis, hepatic adenoma, cirrhosis, and FNH) with appropriate controls.

Results: In the cancer cohort, we demonstrated a 2+ or 3+ staining in 20/25 cases (80%). In the non-cancer cohort, 2+ staining was demonstrated in 2 out of 6 adenoma (33.3%) and 1 out of 6 FNH (16.7%) with no 3+ staining demonstrated. Positive immunoreactivities were also demonstrated in other non-cancer cases. With all cases considered, Fisher's exact test was performed for staining pattern of $\geq 2+$ ($p=0.008$) and 3+ ($p<0.001$). The sensitivity of the $\geq 2+$ staining pattern was 80% with a negative predictive value of 74% to exclude HCC. With the 3+ staining pattern the sensitivity dropped to 52%, but the specificity was 96% and had a positive predictive value of 93% for HCC.[figure1]

Conclusion: Histologic differentiation of an adenoma from a well-differentiated HCC can be challenging. With a strong specificity (96%) and positive predictive value (93%) for a 3+ scoring pattern for HCC, AKR1C3 immunohistochemistry can be an important adjunct to differentiate well-differentiated HCC from benign mimics.



MANAGEMENT OF INTRACRANIAL MENINGIOMAS USING KEYHOLE AND ENDONASAL TECHNIQUES

Presenter: Jacob B. Archer

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Keyhole craniotomies and endoscopic endonasal approaches are being increasingly explored for lesions of the skull base. These techniques have several advantages over the use of traditional large craniotomies, including the reduction/elimination of brain retraction, avoidance of cortical exposure and manipulation, reduced perioperative morbidity, improved cosmesis and faster postoperative recovery / time to discharge. However, patient selection and judicious application of these techniques is essential for optimal patient outcomes, as not all meningiomas are ideal candidates for a keyhole approach. Often, a combination of operative approaches is required for satisfactory tumor resection. We evaluated the technical aspects and discuss surgical nuances of these approaches for management of 28 patients with a total of 32 intracranial meningiomas.

A retrospective review and data collection of all patients treated for intracranial meningiomas by the senior author at this institution using “keyhole” or endoscopic procedures from January 2012 to June 2013 was performed. 28 patients were treated including supratentorial (9 patients), anterior cranial fossa (5 patients), middle fossa (7 patients), posterior fossa (6 patients), complex skull base (5 patients). All but two patients had WHO grade I tumors. The mean operative time for individual approaches for skull-base tumors was 7 hours, 58 minutes (range = 2:55-16:14); mean operative time for supratentorial individual approaches was 4 hours, 20 minutes (range=1:45-7:13). Simpson Resection grades were as follows: Grade I = 5, II = 6, III = 1, IV = 14, V = 0. The mean post-operative hospital stay was 5 days (range = 1-20 days). Eleven patients received adjuvant radiation. The most common presenting symptom was visual loss (36%; n=10), followed by cranial nerve palsies (25%; n=7). In the ten patients with some kind of visual loss, three patients had residual visual deficits postoperatively; the others improved or resolved completely. In those with cranial nerve palsies, all but one patient experienced improvement or resolution of the deficit postoperatively. Four patients experienced new perioperative cranial nerve palsies, all of which were improved or resolved at time of last follow-up.

Our results show satisfactory outcomes with minimal complications, morbidity and no mortality utilizing tailored keyhole approaches for resection of various intracranial meningiomas. With careful preoperative evaluation of the imaging and tumor characteristics, single approaches or a combination of specifically tailored corridors can be utilized to manage a range of lesions from straightforward to extremely challenging locations with satisfactory results.

VISCEROSENSORY AND LIMBIC NEUROCIRCUITRY UNDERLYING THE HEDONIC EVALUATION OF CIGARETTE CUES

Presenter: Jason A. Avery

Jason A. Avery^{1,2}, Kaiping Burrows¹, Kara L. Kerr^{1,3}, Jennifer Dobson¹, and W. Kyle Simmons^{1,4}

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Previous functional neuroimaging research has demonstrated that in smokers, relative to non-smokers, perceiving smoking cues results in activation of reward neurocircuitry, particularly in the orbital and medial prefrontal cortex, as well as the striatum and insula (Nakamura et al 2000, Due et al 2002, Dom et al 2005, Naqvi et al 2010). The extant functional neuroimaging literature has generally used tasks that require passive viewing of smoking cues, and not more deliberative evaluations of the expected hedonic value afforded by those stimuli. Although the motivation to smoke in response to cigarette cues is often non-conscious and automatic, in the context of smoking cessation efforts, smoking cues often trigger deliberative valuation judgments. It is therefore important to understand the neural circuitry involved in more deliberative judgments of smoking cues, as these may play a role in the success of smoking cessation efforts.

To better understand the neural systems underlying these deliberative pleasantness inferences, we modified a task used previously by our lab to examine food pleasantness inferences. In the present study, healthy smokers and non-smokers underwent functional Magnetic Resonance Imaging (fMRI) while rating the expected pleasantness afforded by smoking particular cigarettes pictured in smoking-related images. Brain regions involved in processing the sensory and reward characteristics of cigarette smoking, including the insula, dorsal anterior cingulate cortex, and the caudate nucleus, exhibited significantly greater activation during pleasantness judgments in smokers, relative to non-smokers. Additionally, amplitude modulation regression revealed multiple regions within the brain's reward neurocircuitry where activity was modulated by the magnitude of reported pleasantness inferences. These results demonstrate that the moment-to-moment appraisal of the hedonic properties of cigarettes modulates activity in viscerosensory and limbic brain regions associated with reward representation.

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

BARRIERS AND FACILITATORS OF COLORECTAL CANCER SCREENING BY COLONOSCOPY IN A RURAL NATIVE AMERICAN POPULATION IN OKLAHOMA

Presenter: Hope Baluh, MD FACS

Hope Baluh MD FACS, Chief of Surgery Cherokee Nation W.W. Hastings Hospital Cherokee Nation Health Services

Colon cancers in the Native American population often present at an advanced stage, and therefore have higher mortality rates. Identifying access barriers to colon cancer screening in this population has the potential to improve outcomes in colon cancer treatment.

This study looked at two groups of Native American patients and evaluated their participation in colonoscopy screening by separate surveys. Responses were used to identify motivators and barriers in hopes that systematic changes might be implemented to enhance screening.

To evaluate facilitators and barriers to colonoscopy in Native Americans two distinct surveys were mailed. One survey queried patients who had completed colonoscopy within a 10 month period in 2013, Group I. The second survey was sent to Group II, those patients who failed to show for a colon screening appointments during the same 10 month time frame. While many determinants of screening identified in the returned surveys are similar to those noted in the general population there were elements identified which differ among Native Americans.

Analysis of surveys from Group I revealed several influential components in an individual's decision. The patient's provider, family, and friends may all impact their decision. Analysis of surveys from those who failed to show for screening appointments found this group to have knowledge deficits, competing obligations, and scheduling issues. Addressing these disparities in a culturally sensitive manner could be key to facilitating screening. Changes to enhance screening rates can impact the delays in diagnosis and ultimately improve survival rates seen in this vulnerable and historically neglected population.

AG-311 INDUCES RAPID MITOCHONDRIAL DYSFUNCTION IN TRIPLE NEGATIVE BREAST CANCER CELLS

Presenter: Anja Bastian

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AG-311 is a novel small molecule that induces rapid necrosis in various cancer cell lines and reduces tumor growth *in vivo*. Since most tumors acquire resistance to chemotherapy through mutated apoptotic pathways, new treatments that induce cell death through necrosis may be beneficial. Treatment of triple negative breast cancer (TNBC) and basal-like breast cancer (BLBC) is especially challenging because of their aggressive and metastatic nature, leading to high recurrence and mortality rates. The absence of growth factor receptor for EGFR2/HER-2/Neu and the receptors for estrogen and progesterone render these cancers resistant to conventional endocrine therapy or other available targeted therapy. Therefore, TNBC and BLBC represent an important clinical challenge to develop more effective agents with lower systemic toxicity. Earlier studies in our laboratory showed that AG-311 shows much better activity against *in vivo* tumor growth compared to current therapeutic treatments, thus AG-311 has significant potential to treat chemotherapeutic resistant TNBC and BLBC.

FDA approval of new therapies requires an understanding of the mechanism of action, thus the goal of these studies was to further elucidate the mechanism of AG-311 induced cancer cell death. We previously showed that AG-311 induces necrosis as demonstrated by rapid membrane permeability, membrane blebbing, and lactate dehydrogenase (LDH) release after 1-3 hours of treatment. Even earlier, only 30 minutes after treatment, significant ATP depletion was observed. Since mitochondria are the main source of ATP, we next focused on the effect of AG-311 on mitochondrial function. AG-311 rapidly depolarized mitochondrial membrane potential, which was observed with the aid of the mitochondria specific dyes, JC-1 and TMRM. Studies on isolated mitochondria showed that AG-311 reduced oxygen utilization rate and inhibited the electron transport chain. Stimulation of mitochondrial metabolism by replacing glucose with galactose in the culture media causes cells to upregulate oxidative phosphorylation for ATP production. Breast cancer cells cultured in galactose supplemented media 5 days prior to treatment were more sensitive to AG-311-induced cell death. In addition, calcium uptake by the mitochondria may be involved in AG-311-induced mitochondrial dysfunction. First, an increase in intracellular calcium was observed in the presence and to a lesser extent in the absence of extracellular calcium. Further studies showed that inhibition of the mitochondrial calcium uniporter (MCU) with RU360 significantly reduced AG-311-induced cell death. Together, this indicates that AG-311 is at least partially working through inhibition of mitochondrial metabolism and disruption of mitochondrial potential, initiated by cellular calcium overload.

EXAMINATION OF CANCER PREVENTION AND CONTROL PROGRAMS AT NCI-DESIGNATED CANCER CENTERS

Presenter: Sarah Beck

Sarah Beck, Undergraduate Research Intern, Stephenson Cancer Center

The purpose of this study is to identify and examine cancer prevention and control (CPC) programs at NCI-designated cancer centers with special emphasis on those with a disparities focus. The majority of the data on aims, leadership, membership, and funding was collected from cancer center web pages between January and August 2013. For those CPC programs indicating an emphasis on disparities, data was collected from NIH and NCI web pages listing cancer center and investigator participation in cancer disparities-related funding initiatives. At present, qualitative data is being collected from select program leaders of disparities-focused CPC programs through telephone interviews. The qualitative data will provide greater detail and understanding of the structure and activities of these programs. Preliminary findings thus far indicate an overwhelming majority of cancer centers feature CPC programs, and the majority of these programs encompass research activity that covers the cancer control continuum. As a general rule, the programs emphasizing disparities as a program “theme” or as part of their aims are active participants in three or more of the NIH/NCI disparities-related funding initiatives.

The study has been performed on the University of Oklahoma-Norman campus and OUHSC campus. The work was guided by Dr. Barbara Norton, Assistant Professor of Research. This abstract is being submitted for the Cancer Health Disparities / Prevention and Control track.

VISIBLE/NEAR IR LIGHT AS A TOOL FOR CONTROLLING DRUG RELEASE OF ANTICANCER PRODRUG

Presenter: Moses Bio, PhD

Moses Bio, PhD¹, Pallavi Rajaputra, PhD¹, Gregory Nkepan, PhD¹, and Youngjae You, PhD^{1,2}

¹Department of Pharmaceutical Sciences; ²Department of Chemistry and Biochemistry, University of Oklahoma

Light-controlled release of biologically active compounds (caged compounds) is an excellent tool for spatio-temporal delivery. Unfortunately, its applications have been limited at the cellular level due to the use of non-tissue penetrable UV light. Most recently, tissue-penetrable low energy light (650-800 nm) was suggested for controlling release of active compounds. However, essential chemical tools are lacking in particular for facile conjugation and fast release of active molecules. We first propose 'Click and Photo-unclick Chemistry' of aminoacrylate (β -enamino ester) which can be built readily and cleaved fast by amine-yne and dioxetane reactions after 690 diode laser irradiation.

We designed and synthesized a prodrug of combretastatin A4. Combretastatin A4 was conjugated to a photosensitizer through a photo-cleavable aminoacrylate linker. CMP-L-CA4, CMP = dithiaporphyrin (a photosensitizer) and L = aminoacrylate linker. Two pseudo-prodrugs (CMP-NCL-CA4 and CMP-L-Rh) also were prepared: CMP-NCL-CA4 could not release free CA4 even after the irradiation (NCL = non-cleavable linker) and CMP-L-Rh as a special fluorescence probe that emits bright rhodamine fluorescence only after cleavage of the linker to releases fluorescent rhodamine after the irradiation. *In vitro* study using MCF-7 cells showed the prodrug conjugate CMP-L-CA4 was 5 fold less toxic than parent drug CA4 without NIR laser irradiation $IC_{50D} = 164 \text{ nM} \rightarrow IC_{50P} = 28 \text{ nM}$ which is presumably due to the release of CA4. The dark toxicity and photo toxicity of CMP-NL-CA4 was quite similar $IC_{50D}: 1802 \text{ nM} \rightarrow IC_{50P} = 1063 \text{ nM}$ (CMP-NCL-CA4) since the release of CA4 is not possible. Most exciting result was that CMP-L-CA4 showed better antitumor effects than CMP-NCL-CA4 upon irradiation. This concept of release mediated by singlet oxygen cleavable linker could provide control in term of the quantity, location and time of release of drug. The easy and high yield reaction and the photo-unclick chemistry of aminoacrylate linker can find many applications, not limited to anticancer drugs and prodrugs, for spatio-temporally controlled release of active compounds but delivery vehicles liposomes, polymers, quantum dots, gold nanoparticle, carbon-nanotube etc. This new concept would contribute in moving the caged compounds strategy to the systemic level.

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STAKEHOLDER ENGAGEMENT AS A MODEL FOR COMPREHENSIVE TOBACCO POLICY PLANNING IN OKLAHOMA TRIBAL COMMUNITIES

Presenter: Jessica Blanchard, PhD

Jessica Blanchard¹, PhD; J.T. Petherick², JD, MPH; Heather Basara³, PhD

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Oklahoma's *Executive Order 2012-01* prohibits the use of all tobacco on all state property and explicitly preempts local governments from enacting tobacco bans that are stricter than the state policy. The sovereign status of federally recognized tribes exempts them from this law; as such, Oklahoma's 38 tribal nations are uniquely positioned to stand apart as leaders in the area of comprehensive tobacco policy. The purpose of this presentation is to provide recommendations for employing university-tribal partnerships as effective strategies for comprehensive tobacco policy planning in tribal communities.

Researchers from the University of Oklahoma facilitated a series of working group meetings with key stakeholders representing an Oklahoma tribal nation to develop a comprehensive tobacco policy designed to regulate the use of all commercial tobacco in all owned, leased, and/or occupied properties of the participating tribal nation. This extended period of collaboration facilitated 1) levels of trust between partners and 2) a steadfast commitment to the planning process, ensuring the completion of the plan amid 1) changes to tribal leadership, 2) shifting political support for stricter tobacco policies, and 3) ongoing concerns about economic implications of tobacco restrictions in tribally owned entertainment and hospitality venues. The process of tobacco policy planning in tribal nations is one that involves a multifaceted group of stakeholders whose diverse sets of interests shape the policy planning process in significant ways. The findings of this study provide useful strategies and best practices for researchers hoping to engage tribal communities as partners in tobacco control planning and policy-based research.

IMMUNOLOGICALLY MODIFIED CARBON NANOTUBE: A NOVEL STRUCTURE FOR LASER CANCER THERAPY

Presenter: Wei R. Chen, PhD

Wei R. Chen

Department of Engineering and Physics, University of Central Oklahoma

Using a potent immunostimulant, glycosylated chitosan (GC), as an effective surfactant for single-walled carbon nanotube (SWNT), a novel immunologically modified carbon nanotube, SWNT-GC, was developed (Figure 1). SWNT-GC retains both the photothermal properties of SWNT, as shown in Figure 2, and immunological properties of GC. Furthermore, with a strong binding between GC with SWNT, GC can be carried into tumor cells by the nanotubes (Figure 3). These unique properties make SWNT-GC a potential agent for laser induced, spatially and temporally synchronized photothermal and immunological reactions (Figures 4 and 5) for the treatment of metastatic cancers. In this presentation, the structure of SWNT-GC will be introduced. The photothermal and immunological effects of SWNT-GC will be presented. The possible mechanism of laser-SWNT-GC for treatment of metastatic cancers will also be discussed.

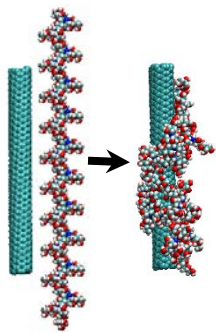


Figure 1. SWNT-GC binding.

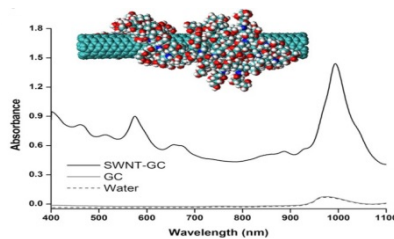


Figure 2. Light absorption spectrum of SWNT-GC.

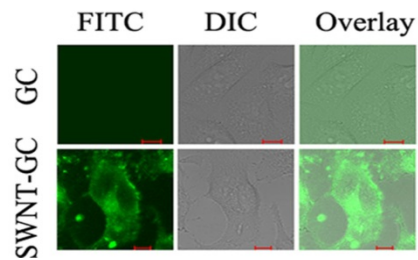


Figure 3. Cellular localization of GC, bound to SWNT.

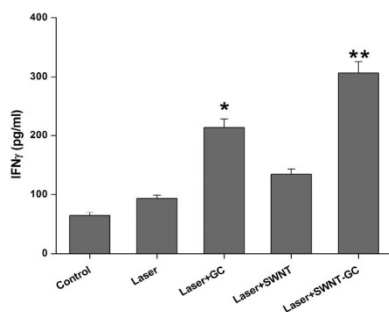


Figure 4. Laser-SWNT-GC induced IFN γ production.

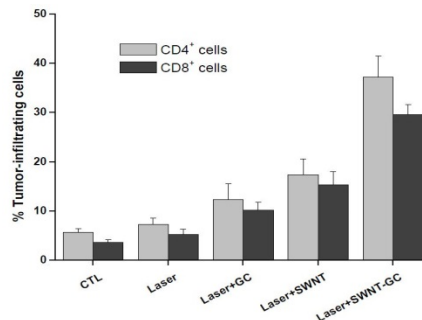


Figure 5. Laser-SWNT-GC induced T-cell infiltration to treated tumor sites.

STUDY THE RELATIONSHIP BETWEEN X-RAY ENERGY SPECTRUM BEAM HARDENING AND THE NOISE POWER SPECTRUM IN COMPUTED TOMOGRAPHY (CT) IMAGES

Presenter: Jason F. Collier

Jason F. Collier, Sulaiman D. Aldoohan and Kamaljit K. Gill

Radiological Sciences Department, the University of Oklahoma, Health Sciences Center

Reducing patient dose while maintaining (or even improving) image quality is one of the foremost goals in CT imaging. However, reduction in dose often comes at the expense of sacrificing image quality, thereby compromising the usefulness of CT scans in clinical diagnoses. Nevertheless, one option of achieving this goal may lie in attempting to reduce the level of noise, as assessed by noise-power spectrum (NPS) analysis, in the acquired images. To this end, we consider optimization of CT scan protocols in conjunction with the application of beam hardening filtration (additional to the inherent filtration of a CT unit) in minimizing patient radiation dose while preserving image quality at a diagnostically acceptable level.

Extra filtration of a given thickness and composition (e.g., copper, tantalum, silver, and brass) of thicknesses range from 25 μm to 250 μm was applied to the inherent filtration of a 64-slice GE CT scanner. Upon recalibration of the system after each filtration application, a uniform electron density slice of an American College of Radiology (ACR) approved phantom was scanned at different scan techniques. This approach was then repeated for the same slice under the same conditions. Next, the two images obtained were subtracted using MATLAB to produce an image of noise. The NPS for this image of noise was then calculated using a MATLAB-based code developed to calculate noise-power spectra. Finally, this NPS was analyzed to assess the image quality associated with the applied filtration via comparison to other applied filtration scenarios.

Noise-power spectra were obtained for additional CT beam-hardening filtrations of various thicknesses and elemental composition. All additional beam-hardening filters showed a decrease in the quanta-noise section of the NPS profile, in the range of 10% to 16% of noise power reduction, when compared with the case in which zero additional filtration was applied. The reduction in the quanta noise section of the NPS profile found in this phantom-based study is encouraging.

LKB1 AS A RAB7 EFFECTOR: IMPLICATIONS FOR THE PRO-ANGIOGENIC RECEPTOR NEUROPILIN-1

Presenter: Kathleen A. Coughlan, PhD

Kathleen A. Coughlan¹, Imoh S. Okon¹, Zitong Wang¹, Joyce Su¹ and Ming-Hui Zou^{1,2}

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Receptor internalization and subsequent degradation is a key biological process in terminating signaling pathways. Importantly, Rab7 is a key regulator in delivering vesicle cargo to the lysosome for degradation. One important co-receptor is Neuropilin-1 (NRP-1) and its availability results in activating signaling pathways including those involved in promoting angiogenesis. Hence, those mechanisms that affect NRP-1 degradation are important. Liver kinase B1 (LKB1), a tumor suppressor gene, has been linked to aberrant angiogenesis however the mechanism(s) are not well defined. Here we demonstrate LKB1 mediates NRP-1 protein degradation via the lysosome. Under serum deprived conditions, NRP-1 accumulates in Rab7 positive vesicles. Furthermore, LKB1 associates with **Rab7Q67L (GTP-bound) more so than Rab7T22N (GDP-bound) suggesting a** novel function for LKB1 as a Rab7 effector, thereby enhancing NRP-1 trafficking from Rab7 endosomes to the lysosome. Lastly, LKB1 mediated degradation was specific for NRP-1, while, the related NRP-2 remained unaffected. Overall this work demonstrates a novel function for LKB1 as a Rab7 effector. Consequently, LKB1 enhances the delivery of NRP-1 from Rab7 positive vesicles to the lysosome thereby attenuating NRP-1 signaling.

**NICOTINE REPLACEMENT THERAPIES, E-CIGARETTES, AND OTHER TOBACCO PRODUCTS:
ASSESSING PERCEPTIONS OF PEDIATRIC AND FAMILY MEDICINE INTERNS**

Presenter: Leslie M. Driskill, M.S.

Leslie M. Driskill^{1,2}, M.S.; ^{1,3}Kristina I. Suorsa^{1,3}, M.A.; ²Tina M. Belt², M.D.; ²Larissa N. Hines², M.D.; ²Julia M. Stoltenberg², M.D.; ²Monique Naifeh², M.D.; Theodore L. Wagener^{1,2}, Ph.D.; Stephen R. Gillaspay^{1,2}, Ph.D.

¹Oklahoma Tobacco Research Center (OTRC), ²University of Oklahoma Health Sciences Center, ³Oklahoma State University

The use and prevalence of e-cigarettes are on the rise and there is little research regarding physicians' attitudes toward the use of these products as either cessation tools or alternatives to smoking. Therefore, this study assessed incoming pediatric (PIs) and family medicine (FMIs) interns' perceptions of e-cigarettes, other tobacco products, and nicotine replacement therapies for use by adolescents and/or parents who smoke. Incoming PIs and FMIs completed questions examining their feelings about e-cigarettes, and the perceived risk of a number of tobacco products, e-cigarettes, and nicotine replacement therapies. Feelings about e-cigarettes were assessed using a 15-item, Likert scale ranging from 1 (Strongly disagree) to 6 (Strongly agree). Ranking of the perceived risk of 12 products was assessed using a Likert scale, with scores ranging from 1 (Extremely harmful) to 10 (Not harmful at all). Twenty-five (82.6%) participants enrolled in the study, with a mean age of 26.7 years (SD=1.83). Sixty eight percent of the sample was female. PIs and FMIs were both "somewhat comfortable" recommending e-cigarettes to adolescents who smoked (M=4.0 and M=3.6, respectively) and parents of pediatric patients (M=4.01 and M=4.00, respectively). When asked to rank the perceived risk of a number of tobacco and nicotine replacement products, mean scores indicated that interns ranked regular cigarettes as the most harmful products (1.12, SD=.44), followed by snuff/dip (1.52, SD=.77), snus (1.71, SD=1.04), dissolvable tobacco (1.88, SD=1.09), pipe tobacco (2.00, SD=1.29), cigars (2.24, SD=1.39), marijuana (3.44, SD=2.53), nicotine inhaler (3.84, SD=2.34), hookah (3.88, SD=2.93), e-cigarettes (5.04, SD=2.23), Nicorette lozenge (5.80, SD=2.04), and Nicorette gum (6.00, SD=1.89). Surprisingly, both incoming PIs and FMIs appear to be somewhat comfortable recommending e-cigarettes to adolescents and parents who smoke. Additionally, interns generally view nicotine replacement products and e-cigarettes to be less harmful than a number of tobacco products, and have a misconception regarding the relative harm of nicotine inhaler vs. either hookah or the e-cigarette.

TGF- β RI INHIBITOR LY2157299 IN UCS PRECLINICAL MODELS

Shailendra Kumar Dhar Dwivedi, PhD

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Uterine carcinosarcomas (UCSs) are highly aggressive, rare, biphasic tumors composed of epithelial (carcinomatous) and mesenchymal (sarcomatous) elements. They arise mainly in the uterus and clinically have a high rate of extra-uterine spread at diagnosis and are responsible for 16.4% of all deaths caused by a uterine malignancy.

UCSs are thought to arise from epithelial and or monoclonal cells therefore sarcomatous regions may represent true examples of complete epithelial-mesenchymal transition (EMT). EMT not only contributes to cancer progression by conferring stem cell-like properties but also increases the cancer cells' resistance towards cell death and chemotherapy. The poor prognosis of UCS may therefore be partly due to its EMT characteristics. Furthermore a recent study demonstrated amplification of the TGF- β 1 locus at 19q13.1 in UCS patient samples, which may contribute to the high expression of TGF- β and thereby the EMT phenotype. We sought to evaluate the importance of TGF- β signaling in UCS and to assess in a pre-clinical model the efficacy of TGF- β receptor I (TGF- β RI) inhibitor in inhibiting proliferation of UCS.

QUANTIFICATION OF DNA DAMAGE CAUSED BY CIGARETTE SMOKE USING PRIMER-ANCHORED DNA DAMAGE DETECTION ASSAY

Presenter: Vengatesh Ganapathy, PhD

Vengatesh Ganapathy¹, Ilangovan Ramachandran¹, ²David A. Rubenstein², Lurdes Queimado^{1, 3-6}
Departments of ¹Otorhinolaryngology, ³Cell Biology and ⁴Pediatrics; ⁵The Oklahoma Tobacco Research Center, ⁶Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, ²Department of Biomedical Engineering, Stony Brook University, New York

Background: Cigarette smoke causes several types of DNA damage and is the main risk factor for lung cancer and head and neck cancer, two of the world's most common malignancies. Secondhand smoke is typically divided into mainstream (MS), the smoke that smokers exhale from their lungs, and sidestream (SS), the smoke emitted from the smoldering end of the cigarette. Cigarette smoke contains a complex mixture of several thousands of chemicals; most of them can induce DNA damage. Detection of DNA damage might provide one of the most accurate biomarkers for cancer risk and prevention studies. However, due to technical limitations, it has not been possible to precisely quantify *in vivo* DNA damage caused by MS or SS smoke. Recently, we developed a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA) to map and quantify *in vivo* levels of DNA damage. In this study, we used this assay to quantify the levels of DNA damage induced by MS and SS smoke.

Aim: To determine PADDA's sensitivity to quantify the *in vivo* levels of DNA damage induced by exposure of human oral cells to escalating doses of MS and SS smoke.

Methods: Human epithelial cells were exposed to escalating doses of MS or SS smoke extracts (0.3, 1.5, 3, 15 and 30µg/ml). DNA damage was quantified in the *p53* gene using q-PADDA at diverse time points. DNA double strand breaks were detected by immunofluorescence analysis of γ H2AX and the cell viability was determined by MTT assay. Data were analyzed by Student's *t* test.

Results: We observed a dose-dependent increase in DNA damage in human oral cells treated with MS and SS smoke extracts. Even 1 h exposure to very low doses of MS or SS smoke resulted in significant DNA damage. We demonstrated that our novel assay PADDA efficiently detects DNA damage in the *p53* transcribed and non-transcribed strands in cells exposed to MS and SS smoke extracts. More interestingly, we observed significant differences in the levels of DNA damage and repair following exposure to MS or SS smoke.

Conclusion: Our study demonstrated that PADDA is a novel and sensitive assay to detect and quantify *in vivo* DNA damage caused by MS and SS. The novel assay validated in this study has potential to be a practical population screening tool for the identification of early biomarkers of susceptibility to tobacco-induced disease, which can guide preventive and diagnostic strategies. More importantly, our study emphasizes the need to support smoking cessation and highlights the importance to prevent or reduce the exposure of non-smokers to second-hand smoke.

INTERPHASE FLUORESCENCE IN SITU HYBRIDIZATION SIGNAL DETECTION BY COMPUTING INTENSITY VARIANCE ALONG THE OPTICAL AXIS

Presenter: Muhammad Ghani

Zheng Li, Bin Zheng, Hong Liu

School of Electrical and Computer Engineering, Univ. of Oklahoma, Norman, OK, USA, 73019

Fluorescence in situ Hybridization technology is a commonly used tool to detect pathological chromosome aberrations. Because of the depth of focus (DoF) constraints of objective lenses with high numerical aperture, automated FISH analysis, which requires reliable and robust automated image acquisition and scan, is frequently conducted with relatively low resolution but sufficiently large DoF to facilitate the depth of the specimen. In this paper, a statistical variance based FISH probe detection scheme is developed in order to address the problem. A stack of image slices are acquired along the optical z-axis under a 100x 1.4 NA objective lens. Statistical variance is calculated along the z-axis to form a 2-D matrix. Since pixels shift dramatically to high intensity at FISH probe locations, the probes will manifest as high peak on the matrix. This experimental data demonstrates that the proposed method is simple but robust for FISH probe detection as well as an alternative representation for three-dimensional data.

Keywords: fluorescence microscopy, extended depth of field, fluorescence in situ hybridization

STUDY THE FEASIBILITY OF RADIATION DOSE OPTIMIZATION IN CT SCANNING PROTOCOLS VIA APPLICATION OF BEAM HARDENING FILTERS

Presenter: Kamaljit K. Gill, MS

Kamaljit K. Gill, MS, Sulaiman D. Aldoohan, PhD, DABR, Jason F. Collier
Radiological Sciences Department, University of Oklahoma, Health Sciences Center

Computed Tomography (CT) imaging became one of the most pivotal scanning technique in modern medicine. The increased usage of CT in routine diagnostic imaging has associated with rise of concerns of increasing risk for radiation-induced cancer. Studies also showed that children are more susceptible to radiation induced cancer than adults. Pediatric hydrocephalus is defined as an excessive accumulation of cerebrospinal fluid (CSF) in the ventricular system, resulting in a high intracranial pressure (ICP). Ventriculo-peritoneal shunting is the most commonly used method for the treatment of pediatric hydrocephalus. CT imaging is the preferred scanning tool in monitoring and evaluating the surgical shunt implementation and any subsequent complications.

The purpose of this research work is to study the feasibility of using different x-ray beam hardening material filters in CT scanner for the intent of reducing pediatric head radiation doses without compromising in image quality. GE CT VCT 64 slices scanner located at the OU Children Hospital was used for this study. Using standard clinical pediatric shunt scanning protocol and the approved American College of Radiology (ACR) CT phantom, image contrast- to- noise ratio (CNR_r) and the effective radiation dose (ED_r) were computed and evaluated. This CNR_r and the ED_r were set as reference indexes for image quality performance and radiation dose adjustment respectively. Additional x-ray beam hardening filters (e.g. copper, tantalum, silver and brass) with different thicknesses range from 25 μm to 250 μm were mounted on the tube assembly. For any added filter, the scanner was calibrated for best image performance.

To have better realistic results, a tissue mimicking phantom called RANDO phantom, which is simulating the human head, were scanned using all scanning protocols associated with different beam hardening filters. Under the condition of maintaining similar CNR values in acquired images, adding copper filter of 1.5 mm thickness exhibited to be the best option to reduce radiation dose, about 25% dose reduction, in comparison to the radiation dose obtained using the existing installed filter. This phantom study showed that significant radiation dose reduction can be achieved in CT pediatric shunt scanning protocols without compromising in the diagnostic value of image quality.

SELECTIVE TARGETING AND TREATMENT OF METASTATIC PANCREATIC CANCER VIA THREE FUSION PROTEIN/PRODRUG SYSTEMS

Presenter: Katrin P. Guillen

Katrin P. Guillen¹, Antonietta Restuccia¹, Carla Kurkjian², and Roger G. Harrison¹

¹Bioengineering Program and School of Chemical, Biological and Materials Engineering, University of Oklahoma; ²Hematology and Oncology Section, University of Oklahoma Health Sciences Center

Pancreatic adenocarcinoma is the 4th leading cause of cancer-related death in both men and women in the United States with a median survival rate <6 months, creating an urgent need for a successful treatment¹. We have developed three novel fusion protein (FP)/prodrug therapies to selectively target and kill pancreatic tumors and their metastases with minimal risk of side effects. Each FP consists of an enzyme with non-human homologs linked to human annexin V (AV). AV serves as the targeting arm due to has a high affinity to phosphatidylserine, an anionic plasma membrane phospholipid which is tightly segregated to the cytoplasmic leaflet in healthy cells but robustly and consistently expressed on the outer leaflet of tumor cells, their metastases, and tumor vasculature². To increase PS exposure/AV binding sites, the cancer cells were treated with a subtoxic doses of docetaxel³. The FP enzymes are: purine nucleoside phosphorylase (PNP) which converts fludarabine (FD) into 2-fluoroadenine (2-FA), L-methioninease (MT) which converts methionine to methanethiol and selenomethionine (SM) to methylselenol, and cytosine deaminase (CD) which converts 5-fluorocytosine (5-FC) to 5-fluorouracil (5-FU). Binding strength of FPs to PS and cytotoxicity of all three systems were evaluated for human Panc-1 and Capan-1 pancreatic cancer cells.

Binding of FPs was strong with K_d ranging from 0.03 to 1.15 nM for Panc-1 cells and 0.02 to 0.90 nM for Capan-1 cells. MT-AV/SM treatment produced complete cell death at concentrations of 500 μ M SM and near complete cell death at concentrations as low as 100 μ M for Panc-1 cells and 85% cell death at 500 μ M SM for Capan-1 cells. PNP-AV/FD treatment was as effective as 2-FA, killing 90% of the Panc-1 cells at a concentration of only 3 μ M FD, while cells treated with FD alone maintained \geq 100% viability after 6 days up to 20 μ M FD. FD treatment alone showed large decreases in cell viability for Capan-1 cells, but PNP-AV/FD treatment showed complete cell killing at 5 μ M FD. CD-AV/5-FC treatment produced 70% cell death at 2000 μ M 5-FC for Panc-1 cells but for Capan-1 cells, CD-AV/5-FC treatment created only 50% cell death at 5000 μ M 5-FC, with no increases in cytotoxic effect seen above 5000 μ M 5-FC concentrations. All three novel FP/prodrug systems show promise for the targeted treatment of pancreatic cancer with minimal side effects.

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MICROPTHALMIA TRANSCRIPTION FACTOR (MITF) AS A DIAGNOSTIC MARKER FOR METASTATIC MELANOMAS NEGATIVE FOR OTHER MELANOMA MARKERS WITH FURTHER COMPARATIVE GENOMIC HYBRIDIZATION ANALYSIS

Presenter: Ruifeng Guo

Ruifeng Guo, Maria Franco-Palacios, Xianfu Wang, Madison Russell, Lindsey Goddard, Elizabeth Gillies, Shibo Li, Kar-Ming Fung, Lewis Hassell
Department of Pathology, University of Oklahoma Health Sciences Center, Department of Pediatrics, Genetics Laboratory, University of Oklahoma Health Sciences Center

Early diagnosis and effective treatment are critical for improved outcome and long term survival for advanced melanoma. Histopathologically, metastatic melanoma has a wide spectrum of morphological patterns and often lacks melanin pigment, which makes immunohistochemical (IHC) characterization necessary. In some cases, the commonly used markers for melanoma (S100, HMB45, Melan-A and Tyrosinase A) are negative in these tumors and makes diagnosis challenging. Correct diagnosis for these cases is critical. Many studies have shown that Microphthalmia Transcription Factor (MITF) has high sensitivity (88-100%) and specificity for metastatic melanoma in addition to the traditional markers mentioned above. Here we reported three cases of high-grade tumor with MITF as the only positive marker pointing to a diagnosis of metastatic malignant melanoma. Subsequent to the diagnoses, previously existing or concurrent primary melanomas were identified in all cases. Comparative genomic hybridization was also performed on one case to further confirm the diagnosis as well as provide more information as for the underlying mechanism. This study revealed multiple shared chromosomal abnormalities in both the primary and metastatic lesions, as well as chromosomal changes specific to the metastasis.

LPA STIMULATE EMT OF OVARIAN CANCER CELLS VIA *gip2* AND *gip* ONCOGENES

Presenter: Ji Hee Ha

Ji Hee Ha, Jeremy Ward, and Danny Dhanasekaran

Peggy and Charles Stephenson Cancer Center and Department of Cell Biology, University of Oklahoma Health Sciences Center

Ovarian cancer is currently the most fatal gynecological cancer with a 5-year survival rate of only 45%. Recent studies have identified a critical role for lysophosphatidic acid (LPA) in the genesis and the progression of ovarian cancer. In order to identify transcription factors that are induced by LPA, a commercial pathway reporter array was used. Hypoxia induced factor 1 (HIF-1 α) induction was the most prominent response showing more than 150 fold transcriptional activation compared with control. LPA treatment under normoxic and hypoxic (1% O₂) conditions increased HIF-1 α protein level, which leads to epithelial-to-mesenchymal transition (EMT) in the ovarian cancer cell line OVCA432. We also found that stimulation of the OVCA432 cells with LPA at normoxic and hypoxic conditions led to a significant increase of the mRNA and protein expression of the EMT transcription factor Twist. Immunofluorescent imaging confirmed that Twist levels were significantly up-regulated and that Twist was translocated to the nucleus as early as 4 hours after stimulation with LPA in both a normoxic and hypoxic environment. Additionally, immunofluorescent imaging showed that expression of E-cadherin on the periphery of the cell as well as in the whole cell was greatly reduced when cells were stimulated with LPA in normoxic and hypoxic conditions. Finally, our study demonstrated that LPA-mediated induction of EMT required both *gip2* and *gip* oncogenes. Overall, our study indicated that the downstream components regulated by oncogenic G-proteins could potentially be targeted in the future to prevent EMT in ovarian cancer.

DOCOSAHEXANOIC ACID ALTERS THE RNA CONTENTS AND SECRETION OF BREAST CANCER EXOSOMES

Presenter: Bethany Hannafon

Bethany Hannafon¹, William Berry², Ralf Janknecht², William Dooley³ and Wei-Qun Ding¹

¹Department of Pathology, ²Department of Cell Biology, ³Department of Surgery, University of Oklahoma Health Sciences Center

Docosahexaenoic acid (DHA), a long chain n-3 polyunsaturated fatty acid, is known to have anticancer activity, however the specific molecular mechanisms of DHA's anticancer action remain elusive. Recent studies have demonstrated that DHA inhibits tumor angiogenesis and metastasis in experimental model systems. The intercommunication between cancer cells and their surrounding microenvironment is essential to tumor angiogenesis and metastasis. Exosomes are membrane-derived extracellular vesicles that are important mediators of intercellular communication, as they can transfer cancer-promoting components to a recipient cell or can be released into the circulation to act at distant sites. However, very little is known about the role of breast cancer derived-exosomes and their contents in contributing to this process, and whether these exosomes mediate DHA's anticancer action.

To address this question, breast cancer cell exosomes were collected from the cell culture media of MCF7 and MDA-MB-231 breast cancer cell lines. The isolated exosomes were verified by electron microscopy, immunogold labeling, and by immunoblot analysis of CD63 (a marker of exosomes). To determine whether DHA alters exosome secretion, we generated a stable line of MCF7 and MDA-MB-231 cells that express GFP-tagged CD63. Upon treatment of the cells with 100 μ M DHA for 24 hours, we observed a >2-fold increase in exosome secretion as measured by the CD63-GFP levels in the purified exosomes from the conditioned media, which was confirmed by analysis of exosome protein concentrations. To understand whether DHA alters the contents of breast cancer-derived exosomes, MCF7 cells were treated with 100 μ M DHA for 24 hours, total RNA was extracted and analyzed by small RNA sequencing. We found that exosomal RNAs are primarily small RNAs, with size ranging from 25 to 1000 nucleotides, consistent with previous reports. Furthermore, the expression of only 6 microRNAs in cells treated with DHA were changed, whereas the expression of 91 microRNAs were altered by DHA in the MCF7-derived exosomes, 83 of which had 2-fold or greater changes. Expression of all but 1 of the 83 microRNAs was up-regulated by DHA treatment. Five of the most abundant exosomal microRNAs (miR-23b, miR-27a/b, miR-21, let-7, and miR-200b) have known anti-angiogenic and anti-metastatic activity. When we applied DHA-treated MCF7 cell exosomes to endothelial cell cultures, the tube formation by endothelial cells (an *in vitro* angiogenesis assay) was significantly inhibited, suggesting that breast cancer cell-derived exosomes mediate DHA's anti-angiogenic action. Our data thus demonstrate that DHA alters breast cancer exosome secretion and contents and that breast cancer exosomes can be manipulated in order to influence their effects on cells in their surrounding microenvironment.

CHEMISTRY, MANUFACTURE AND CONTROLS (CMC) OF SHetA2 CAPSULES FOR FDA APPROVAL OF PHASE 0 CLINICAL TRIALS

Presenter: Mariam Ibrahim

Mariam Ibrahim, Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center

Introduction: SHetA2 is a flexible heteroarotinoid that reverses the cancerous phenotype and induces cell apoptosis. Oral administration of SHetA2 inhibited the growth and size of tumors in the Rat MNU mammary cancer model and the APCmin/+ mouse model of intestinal tumorigenesis. Formal toxicological studies did not show any adverse effect supporting the advancement of this drug to clinical trials. However, SHetA2 is highly hydrophobic and it has poor oral bioavailability without Kolliphor HS15. Previously, we dispersed SHetA2 in Kolliphor and fill it in hard gelatin capsules for oral administration. Unfortunately, this formulation in individual capsules exhibited large variability in drug content and dissolution timing. In this study, we developed a new dry, loose powder SHetA2 formulation to be dosed in the capsules. Due to the 'lipophilic' nature of the drug, powders were prepared by a novel spray freeze drying technique. SHetA2 capsules were subjected to quality control tests required by the United States Pharmacopeia (USP).

Methods: SHetA2 was probe sonicated with melted Kolliphor HS15. A trehalose solution was then added to the mixture and homogenized at a speed of 13,500 rpm for 2 minutes. The homogenized mixture was then spray freeze dried using Buchi Mini spray dryer B-290 at feed rate of 4ml/min, flow rate of 45 and 5 mBar pressure in 2 liquid nitrogen. The frozen droplets were kept for 2 hours at -80 °C then freeze dried for 48 hours. Capsules of Size 000 were filled manually with 680 mg of the prepared formulation equivalent to 170 mg of SHetA2 and stored in tightly closed light protective containers. The following tests were performed: drug content uniformity, weight variation, disintegration test and dissolution test. Quality control tests were performed in the final product and in process according to USP guidelines.

Results: The mean SHetA2 content in the bulk powder was 5.8 ± 0.52 . The individual capsule content was 90-110% of the target weight. Thus, we can be sure that the accurate dose will be delivered to each patient. The mean disintegration time was 17.33 ± 2.3 minutes and capsules released their content within 30 minutes. The percentage of drug dissolved in simulated gastric fluid (SGF) was $69.2\% \pm 33.00$ and $54.17\% \pm 29.02$ in simulated intestinal fluid (SIF). Based on in-vitro-in-vivo correlations, it is predicted that the percent of drug solubilized would be the approximate bioavailability in a patient.

Conclusion: The formulated SHetA2 capsules have fulfilled the requirements of USP for immediate release capsules making them acceptable for administration to patients in phase 0 clinical trials. The results of the powder manufacture and quality control performed in this study are part of the New Drug Application (NDA) package that has been submitted for FDA approval.

IDENTIFICATION OF POTENTIAL VEGF-DEPENDENT BIOMARKERS FOR RESPONSE AND RESISTANCE TO ANTIANGIOGENIC THERAPY

Presenter: Pharavee Jaiprasart

Pharavee Jaiprasart, Bharat Devapatla and Sukyung Woo

Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center

Antiangiogenic therapy targeting vascular endothelial growth factor (VEGF) pathway has been proven to be beneficial for increasing progression-free survival of cancer patients. However its clinical benefits seem to be transient and unpredictable. The major challenge is to identify biomarkers for early detection of resistance to anti-VEGF therapy. Here, we report our progress in identifying VEGF-dependent vasculature (VDV) biomarkers from mRNA profiling of tumor and stroma following anti-VEGF treatments in xenograft mice.

Athymic nude mice implanted with SKOV3 cells received bevacizumab (10 mg/kg, ip, BIW), sorafenib (30 mg/kg, po, QD), or saline (po, QD) for 2 months. Tumor volumes were measured twice weekly using caliper. Tumors that showed long-term trend toward continued tumor progression during treatments after an initial response were considered treatment-resistance. In contrast, treatment-sensitive tumors were defined by a long-term trend toward stable disease or regression. At the end of the study, tumors were collected from each group for gene profiling using Illumina next-generation sequencing analysis. The data analysis was performed using GeneSifter (Geospiza, Seattle, WA) based on pair-wise analysis, student t-test, and P value < 0.05 is considered statistically significant.

We compared expressions of genes involved in tumor vasculature responses to VEGF (VDV) between treatment-sensitive and –resistant groups. The VDV gene expressions in tumor stroma, but not in tumor cells were strongly altered in treatment-resistant groups. We found that *Aplnr*, *Apln*, *Sema3f*, *Gbp4*, *Kcne3*, *Mcam*, *Cd34*, *Lama4*, *Prnd*, *Nid2*, and *Rgs5* showed resistant marker signatures while *Esm1*, *Col4a1*, *Col4a2* and *Egfl7* showed response marker signatures. A significant down regulation of *Gbp4* in the bevacizumab-resistant group (P<0.001) seemed to indicate its tumor suppressor role. Microvascular proliferation markers, *Aplnr* (apelin receptor) and its ligand (*Apln*), were significantly upregulated in sorafenib-resistant tumors compared to those in sensitive tumors (P<0.0005), indicating restoration of neovascularization in resistant tumors.

We have identified a set of VDV genes correlated with tumor vasculature responses and resistance, and their changes in expressions upon long term treatment of anti-VEGF therapy signify their potential as biomarkers for tumor resistance to anti-VEGF therapy.

LONGITUDINAL EVALUATION OF THE TOBACCO STOPS WITH ME CAMPAIGN

Presenter: Shirley James, MS

Shirley James¹, MS, Rebekah R. Rhoades¹, MPH, Nasir Mushtaq¹, PhD, Sjonna Paulson², APR, and Laura A. Beebe¹, PhD

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Introduction: The primary aim of this study was to evaluate the Tobacco Stops With Me (TSWM) health communications campaign in Oklahoma by determining awareness and impact on tobacco-related attitudes, knowledge and behavior among both tobacco users and non-users.

Methods: This multi-phase health communications campaign was initiated by the Oklahoma Tobacco Settlement Endowment Trust in partnership with the Oklahoma State Department of Health. To evaluate its success a 2-year longitudinal study of 4001 Oklahomans ages 18-54 was conducted by the University of Oklahoma Health Sciences Center, College of Public Health, Department of Biostatistics and Epidemiology, in collaboration with Westat, a survey research firm located in Rockville, MD. Baseline data were collected through landline and cellular phone contact in 2007 prior to the launch of the campaign, followed by two additional surveys at 1-year intervals. Data were analyzed using methods appropriate for weighted data.

Results: Overall campaign awareness was highest among tobacco non-users (83%), whites (83%), college graduates (86%) and those ages 25-34 (84%). Exposure to TSWM doubled quit attempts among tobacco users and increased knowledge about the harms of SHS in tobacco users and non-users. Tobacco non-users exposed to TSWM were 1.5 times more likely to help someone quit using tobacco than those not exposed. Tobacco non-users exposed to TSWM were more likely to report that tobacco is a serious problem in Oklahoma, believe that tobacco companies should not be allowed to give away free samples or advertise at public events, and believe that smoking should be banned at public outdoor places. These findings were statistically significant and independent of competing explanations.

Discussion: This study is one of few that have incorporated a longitudinal design and a cell phone sample to evaluate the impact of a statewide tobacco counter marketing campaign. It demonstrated campaign impact on tobacco-related attitudes, knowledge and behaviors among both tobacco users and non-users.

RALOXIFENE AND GONADERELIN INHIBIT COLON TUMORIGENESIS BY DECREASING STEM LIKE CELLS AND INCREASING NATURAL KILLER (NK) CELLS

Presenter: Naveena B. Janakiram, PhD

Naveena B. Janakiram¹, Altaf Mohammed¹, Misty Brewer¹, Taylor Bryant¹, Laura Biddick¹, Stan Lightfoot¹, Gopal Pathuri^{1,2}, Hariprasad Gali², and Chinthalapally V.Rao¹.

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Clinical and Preclinical studies suggest that estrogen plays a contributing role in colorectal cancer (CRC). This project examined the tumor inhibitory effects of raloxifene, a selective estrogen receptor modulator (SERM), and gonadorelin, an anti-estrogenic drug, in female *Apc*^{Min/+} mouse intestinal tumorigenesis. Six-week-old *Apc*^{Min/+} mice were fed modified AIN-76A diet containing 1 ppm raloxifene or control diet. Gonadorelin (150ng/mouse) was injected subcutaneously into one treatment group. Intestinal tumors were evaluated for tumor multiplicity, location and size. Mice treated with raloxifene and gonadorelin showed colon tumor inhibition of 80% and 75% respectively. Both drugs significantly inhibited small intestinal tumor multiplicity and size (75 – 65%, $P < 0.0001$). Raloxifene and gonadorelin showed significant tumor inhibition with 98% and 94% inhibition of polyps >2 mm in size. In mice fed with raloxifene or injected with gonadorelin, tumors showed significantly reduced proliferating cell nuclear antigen expression (58-65%, $P < 0.0001$), decreased laminin-1 β , and decreased stem like cells (Lgr 5, EpCAM, CD44/CD24), as well as suppressed inflammatory genes (COX-2, 5-LOX, iNOS), or increased chemokines required for NK cells. Both drugs were effective in suppressing tumor growth albeit with different mechanisms. Raloxifene tumor inhibitory effect is by inhibition of β -catenin signaling, whereas gonadorelin was effective by inducing NK cell cytotoxicity against intestinal tumorigenesis. These observations show that either suppression of estrogen levels by gonadorelin or modulation of estrogen receptor by raloxifene dramatically suppresses small intestinal and colonic tumor formation in female *Apc*^{Min/+} mice. These results support the concept of chemoprevention by these agents in reducing endogenous levels of estrogen or modulating ER signaling.

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PRIMARY VENOUS THROMBOEMBOLISM PROPHYLAXIS IN PATIENTS WITH SOLID TUMORS RECEIVING CHEMOTHERAPY: A META-ANALYSIS

Presenter: Sonia John

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Background: Venous thromboembolism [VTE] is the second highest cause of mortality among patients with cancer. However, pharmacological thromboprophylaxis for patients with solid tumor is only recommended during hospitalization. Primary outpatient thromboprophylaxis is not a widely accepted practice.

Objective: Determine safety and efficacy of outpatient primary VTE prophylaxis in patients with solid tumors.

Data sources: A systematic review was conducted using MEDLINE and EMBASE up to June 2012. Key search words included venous thromboembolism, malignancy, anticoagulants, and chemotherapy. Studies were considered for our meta-analysis if they included outpatient primary pharmacological thromboprophylaxis in adult patients with active solid cancer. All the information was independently reviewed by 2 of the authors [MP, SJ] and a third reviewer resolved discrepancies. The measure of association was calculated with R (R: A Language and Environment for Statistical, R Development Core Team, www.R-project.org), R META package (Version 0.8-2, Author: Guido Schwarzer). The Q statistic was calculated and a formal test of homogeneity was conducted. Random-effects model was preferred in case of heterogeneity.

Results: A total of 1371 abstracts were reviewed and 29 manuscripts were fully abstracted. Eight randomized controlled trials including 6706 patients were analyzed. There were less VTE events with outpatient prophylaxis: odds ratio [OR] of 0.53 (95% CI, 0.40-0.70). Six studies used low or ultra-low molecular weight heparin and two studies used warfarin. In the subgroup analysis of heparin based primary prophylaxis, there was a significant reduction in VTE events [OR 0.47, 95% CI, 0.34-0.64], no significant heterogeneity [FIG 1]. In addition, there was no difference in major bleeding events between groups [OR 1.48, 95% CI, 0.89-2.46]. Five studies reported mortality data; there was significant heterogeneity between studies.

Conclusions: Heparin based outpatient VTE prophylaxis in patients with solid tumors reduced by half the risk of VTE with no significant differences in major bleeding events. The current publications do not allow a meaningful grouped analysis of survival data, improved patient selection is necessary in order to adequately target VTE prevention strategies.

RECRUITMENT AND RETENTION OF AMERICAN INDIAN SMOKERS INTO A CULTURALLY-TAILORED SMOKING CESSATION STUDY

Presenter: Melanie Johnson, MEd

Melanie Johnson, MEd, Research Project Coordinator; Michelle Hopkins, BA and Laura Beebe, PhD,
Oklahoma Tobacco Research Center, University of Oklahoma Health Sciences Center

American Indians have the highest smoking rates of the major racial/ethnic groups in the United States. Furthermore, this underserved population has very low smoking cessation and abstinence rates. To date, few studies have focused on methods to encourage smoking cessation among American Indian smokers. The current study is an ongoing group randomized controlled trial to examine the efficacy of a culturally-tailored smoking cessation program, "All Nations Breath of Life." This multi-site study is collaboration between the Oklahoma Tobacco Research Center, the University of Kansas Medical Center, the Choctaw Nation of Oklahoma, the Seven Tribes of Southwest Oklahoma, and the Indian Health Service. The recruitment goal for Oklahoma was 28 groups of 8 smokers randomized to the tailored or non-tailored intervention for a total sample size of 224 American Indian smokers. We will present recruitment strategies and discuss the barriers for recruitment and retention in this population.

The quarterly recruitment target for this study was 24 participants and of the 10 quarters of potential recruitment, we reached the target in only 4 of the quarters. Initial delay in the recruitment of participants was related to the time required to obtain tribal and IRB approvals. In addition, we encountered challenges related to identifying and training of facilitators. Finally, the delay from initial screening to randomization of participants caused some smokers to lose interest in the program, which also impacted recruitment. The major reasons for lack of retention in the study included phone numbers being disconnected, change of home addresses and/or phone numbers, child/family care responsibilities, transportation, intensity of the program (especially first 3 months), and coordination of the meeting day/time for each group member. Although we will reach our enrollment target of 224 total American Indian smokers, delays in the initial recruitment and maintenance of our target recruitment rate have presented challenges in conducting this study. Lessons learned from these challenges will inform future studies with this priority population.

PREVENTION OF BREAST CANCER LUNG METASTASIS VIA THE BLOCKADE OF THE ADHESION CASCADE

Presenter: Shin-Ae Kang, PhD

Shin-Ae Kang¹, Nafis Hasan², Stephen K. Suh³, Hallgeir Rui², Takemi Tanaka¹

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Organ metastasis is a major cause of mortality from breast cancer. In particular, lung metastasis occurs frequently in hormone independent breast cancer patients. Yet, therapeutic options for lung metastasis are limited and largely palliative. Therefore, a novel therapeutic strategy for metastatic breast cancer is urgently needed. Hematogenous metastasis occurs when disseminated cancer cells adhere to the surface of blood vessels and extravasate through the vascular endothelium of distant organs. The adhesion of circulating cancer cells to the vascular endothelium is a rate limiting process and is initiated by E-selectin (also known as CD62E, ELAM-1 or LECAM-2). E-selectin is selectively expressed in inflamed vascular endothelium and mediates a rolling adhesion of circulating cells to a firm adhesion to the vascular endothelium through the binding to its ligand present on the disseminated cancer cells. Therefore, the functional blockade of E-selectin is expected to block the adhesion of circulating cancer cells to the vessel surface and subsequent tissue migration. We have recently developed an antagonistic thioaptamer against E-selectin (ESTA). This compound has a high affinity to E-selectin ($K_d=47$ nM) and antagonistic activity ($IC_{50}=63-80$ nM). In this study, we aim to dissect the vascular adhesion mechanism of breast cancer cells with an ultimate goal of developing a new therapeutic strategy for the inhibition of lung metastasis via the blockade of the adhesion cascade using ESTA.

We demonstrated that E-selectin enhanced the adhesion and transendothelial migration in hormone independent basal like ER-/CD44^{high} breast cancer cell lines (MDA-MB-231 and MDA-MB-468), but not in luminal like ER+/CD44^{or low} breast cancer cell lines (MCF-7 and T-47D). To seek the mechanism of preferential adhesion of hormone independent breast cancer cells to E-selectin-expressing endothelium, we searched for a possible ligand exclusively present on hormone independent breast cancer cells. Our data demonstrated that 1) E-selectin physically binds to a variant form of CD44 (CD44v) from MDA-MB-231 cells, 2) CD44 blocking antibody or shRNA knockdown of CD44 in cancer cells inhibited their adhesion to E-selectin-expressing endothelial cells. These data indicated that CD44 functions as a ligand for E-selectin and mediates the adhesion of CD44+ breast cancer cells to endothelial E-selectin. Finally we evaluated the effect of ESTA using three independent mouse models of metastatic breast cancer. Our data demonstrated that a single intravenous administration of ESTA reduced the formation of lung metastases in mice injected with CD44+ breast cancer cells with no overt toxicity. The effect of ESTA, however, was minimal on lung metastasis formation of CD44 knocked-down cells, suggesting that the functional blockade of E-selectin may be selectively effective in CD44+ breast cancer, but not in CD44-.

In conclusion, CD44 (CD44v) is a functional ligand for E-selectin. The E-selectin antagonist (ESTA) effectively inhibited the formation of lung metastases of CD44+ breast cancer cells, further highlighting the feasibility of targeting the adhesion cascade for the prevention of breast cancer lung metastasis.

CD55 MEDIATED PATHOGENESIS OF INVASIVE *E. COLI* IN HUMAN HEPATOMA (HUH-7) CELL LINE: AN IN VITRO MODEL OF INFLAMMATION INDUCED CARCINOGENESIS

Presenter: Rashmi Kaul, PhD

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About 80% of hepatocellular carcinomas (HCCs) develop in fibrotic or cirrhotic livers as a consequence of chronic liver injury (Luedde and Schwabe, 2011). We recently reported the presence of various aerobic bacteria including *E. coli* in normal and cirrhotic liver tissues and demonstrated that in spite of the increased bacterial colonization in normal liver tissues compared to cirrhotic livers there was maintenance of suppressed inflammation and immune tolerance in normal livers (Singh et al, 2011). Increasing evidence suggests that chronic inflammation precedes malignancy, however the pathways of inflammation that may be responsible for high rate of HCC development in chronically injured or fibrotic livers remain largely unknown.

To evade innate immunity, virulent pathogens utilize host cell receptors that are involved in innate immunity and modulate the development of inflammation. CD55, a complement regulatory protein that limits excessive complement activation on host cells is also utilized as a cellular receptor for colonization by several pathogenic organisms including uropathogen Dr adhesin bearing *E. coli* (Dr⁺ *E. coli*). CD55 is reported to be elevated in various cancers allowing cancerous cells to escape complement mediated cytotoxicity. Dr⁺ *E. coli* are invasive bacteria with high translocation potential and are associated with chronic urinary tract infections (UTI) and diarrheal diseases. In a mouse model of experimental UTI using Dr⁺ *E. coli*, we demonstrated the translocation of Dr⁺ *E. coli* to other organs, including liver.

In the present study, we compared the bacterial colonization and invasion by Dr⁺ *E. coli* in primary human hepatocytes and the human hepatoma cell line, Huh-7 using gentamicin protection assay. We further investigated whether Dr⁺ *E. coli* utilizes CD55 as a receptor for internalization. Our results demonstrate that Dr⁺ *E. coli* was able to invade hepatoma cells more efficiently (invasion index 0.996 ± 0.15) than primary hepatocytes (invasion index 0.193 ± 0.03). This internalization of bacteria was dependent on the polymerization of actin and microtubules as pretreating the cells with cytochalasin D and nocodazole resulted in decrease in bacterial invasion by 42% and 38% respectively. Activation of p38 and MEK1 kinases was also required for internalization of Dr⁺ *E. coli*. Inhibition of p38 by SB202190 and MEK1 by PD98059 resulted in ~50% reduction in bacterial internalization. We were further able to significantly reduce bacterial invasion by preventing binding of bacteria to CD55 after pretreating cells with an anti-CD55 antibody, prior to infection. This, new *in vitro* cell model of Dr⁺ *E. coli* invasion in Huh-7 cells, will serve as a novel model to study the host pathogen interaction resulting in inflammation induced liver carcinogenesis. [Cancer Sucks, Bixby, OK; OSU-CHS Intramural Grant; NIH Liver Tissue procurement and Distribution System (DK92310)].

RADIATION INSTIGATES EMT, CSC SELF RENEWAL AND PLURIPOTENCY SIGNAL TRANSDUCTION IN NON-TARGETED (BYSTANDER) ER α ⁺ AND TRIPLE-NEGATIVE BREAST CANCER CELLS

Presenter: Faizan H. Khan

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Ascertaining radiation-induced bystander response in non-targeted tumor cells, particularly on variables pertaining to resistance, relapse and tumor progression, may escort significant clinical implications. Accordingly, in this study, we investigated the radiation induced alterations in factors that drive the epithelial-to-mesenchymal transition (EMT), cancer stem cells (CSCs) self-renewal capacity and pluripotency maintenance in non-targeted breast (ER α ⁺ MCF-7 and triple-negative MDA-MB-468) adenocarcinoma cells. Co-cultures of non-targeted breast cancer cells with irradiated (5Gy) counterparts for 24h were assessed for transcriptional regulation of 93 stem cell related molecules using QPCR profiling. Radiation-induced alterations in the expression of ABCG2, E-Cadherin, N-Cadherin, MYC, Nanog and SOX2 in bystander MCF-7 and MDA-MB-468 were assessed using western blot analysis. Radiation profoundly increased the transcriptional activation of stem-cell related molecules in distant bystander ER α ⁺ MCF-7 (70 genes) and in triple-negative MDA-MB-468 (82 genes) cells. Interestingly, 62 of 70 genes activated in MCF-7 and 81 of 82 genes in MDA-MB-468 showed significant (>2 fold) upregulation. Evidently, radiation induced 66 genes (>2 fold, 58 genes) in bystander breast cancer cells independent of their hormone status. Consistently, immunoblotting revealed increase in the expression of ABCG2, N-Cadherin, MYC, Nanog and SOX2 in both MCF7 and MDA-MB-468. Together, these data demonstrates that radiation activates the EMT, CSCs self-renewal and pluripotency maintaining factors in non-targeted bystander cells and could thus play an instrumental role in breast cancer relapse and progression.

ERLOTINIB IS NOT EFFECTIVE IN PATIENTS (PTS) WITH JAK-2 V617F POSITIVE POLYCYTHEMIA VERA

Presenter: Mohamad Khawandanah, MD

Mohamad Khawandanah, MD¹, Zhizhuang Joe Zhao², Samer Srour, MB ChB¹, Howard Ozer, MD, PhD³, George Selby, MD¹, Bassam Ghabache, MD¹ and Mohamad Cherry, MD¹.

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Introduction: Erlotinib is an epidermal growth factor receptor small-molecule inhibitor and is FDA approved for the treatment of lung and pancreatic cancers. In preclinical study, *in vitro* colony culture assays revealed that erlotinib at micro-molar concentrations effectively suppressed the growth and expansion of Polycythemia Vera (PV) hematopoietic progenitor cells while having little effect on normal cells. Several JAK inhibitors are being studied for the management of PV, one of which has been approved for the treatment of myelofibrosis (ruxolitinib). **Aim:** To study the clinical effect of erlotinib in pts diagnosed with JAK2V617F + PV. **Methods:** We conducted a single arm, prospective phase II study at the University of Oklahoma and the Oklahoma City VA hospitals in pts with WHO defined JAK-2 V617F positive PV from June 2010 to August 2012. Appropriate IRB approval was obtained in accordance with Helsinki declaration. Pts had to be requiring phlebotomy. Toxicity was assessed by treating physicians using NCI version 4. Dose modification for erlotinib was done using label recommendations. **Results:** Five Caucasian pts were enrolled (3 (60%) males, with median age of 63 years, range 26-79). Pts had pretreatment median hemoglobin 14.4 g/dL (10.4 -19.2 g/dL), median platelet count 511 x10⁹ (424-681 x10⁹), median white blood cell (WBC) 14.4 x10⁹ (7.8- 18.3 x10⁹). Three pts had splenomegaly prior to treatment. Median number of prior pharmacologic treatments (hydroxyurea, anagralide or interferon) was 1, range 0-2. Pts were given erlotinib 150 mg orally daily for 16 weeks: responders (phlebotomy free or decrease in spleen size) were allowed to continue a total of 1 year treatment, while non-responders were taken off the study. Three (60%) patients received therapy for 16 weeks and did not achieve hematological response or improvement in spleen size. Two (40%) pts were taken off the study after 2 doses secondary to severe toxicities (grade 3 colitis in 1 case, and grade 2 facial rash in 1 case). No therapy continued beyond 16 weeks (due to toxicity or lack of response). All pts in the study developed rash (grade 1 – 3) and diarrhea (grade 1 – 2). Three pts developed mucositis (see Table 1). No death was observed during the study and follow up period (median follow up was 23 months, range 37-12). Study was closed due to lack of efficacy. **Conclusions:** Despite *in vitro* efficacy of erlotinib as potent inhibitor of JAK-2 activity, erlotinib is not effective in pts with JAK-2 V617F positive PV with poor toxicity profile. Poor accrual was related to potential toxicity of erlotinib compared to alternative treatments in view of lack of clinical efficacy. Our study was closed to accrual.

Table 1: CTCAE version 4 grades of toxicities

Patient	Diarrhea	Rash	Mucositis	Fatigue	Nausea	Abdominal pain	Other
1	1	2	1	0	0	0	-
2	2	0	0	0	2	2	Colitis (3)
3	2	3	2	0	1	0	-
4	1	3	2	1	1	0	Cellulitis (3)
5	1	1	2	1	0	0	Esophagitis (1), Black hairy tongue.

DOWN-REGULATION OF ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP) 1B3 FUNCTION BY PROTEASOME INHIBITOR BORTEZOMIB

Presenter: Alam Khondoker

Alam Khondoker, Alaa Abuznait and Wei Yue

Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center

Purpose: Organic anion transporting polypeptide (OATP) 1B3 is a liver-specific membrane transport protein under normal physiological condition, while often aberrantly expressed in many cancers. OATP1B3 transport many drugs (*e.g.*, statins, paclitaxel and docetaxel); cholecystokinin-8 (CCK-8) is a specific OATP1B3 substrate. Altered OATP1B3 transport activity is associated with altered pharmacokinetics, efficacy, and toxicity of drugs that are OATP1B3 substrates. To date, limited information exists about the regulation of the transport activity of OATP1B3. This study aimed to determine the role of the ubiquitin-proteasome pathway in OATP1B3 degradation and to assess the impact of proteasome inhibitor bortezomib, a first-in-class anticancer drug, on OATP1B3 transport activity in both primary human hepatocytes and cancer cell lines.

Methods: Human sandwich-cultured hepatocytes (SCH) and HeLa cells transiently expressing OATP1B3 were treated with bortezomib (100 and 250 nM) and vehicle control (DMSO) for up to 7 h. To determine the effect of proteasome inhibition on transport activity of OATP1B3, accumulation of [³H]CCK-8 (1 μM, 3 min) were compared between bortezomib and control treatments. Immunoblot of ubiquitin was utilized to determine the efficiency of proteasome inhibition, and of OATP1B3 to determine protein levels of OATP1B3.

Results: In human SCH, ubiquitin-conjugated proteins were markedly increased in bortezomib-treated cells compared to control, consistent with efficient proteasome inhibition by bortezomib. Bortezomib treatment in human SCH results in ~1.4-fold increase in OATP1B3 protein levels, while unexpectedly resulting in 1.5-2-fold decrease in CCK-8 accumulation. Bortezomib treatment also significantly decreased OATP1B3-mediated CCK-8 transport by ~2.1 fold in HeLa cells transiently expressing OATP1B3.

Conclusions: Proteasome inhibition by bortezomib down-regulates transport function of OATP1B3 both in primary hepatocytes and in cancer cells. Increased OATP1B3 protein levels following proteasome inhibition suggest that the ubiquitin-proteasome pathway is involved in OATP1B3 degradation. The inverse correlation between OATP1B3 protein levels and transport function implies ubiquitination of OATP1B3 may affect trafficking of OATP1B3 to the cell surface. These findings provide a novel mechanism in regulating OATP1B3 function in liver and in cancers. This study also highlights the clinical significance of proteasome inhibition as a potential determinant for OATP1B3-mediated DDIs affecting pharmacokinetics and efficacy of anti-cancer drugs (*e.g.*, paclitaxel) that are OATP1B3 substrates.

IMPACT OF THE HISTONE DEMETHYLASE JMJD2A ON PROSTATE CANCER DEVELOPMENT

Presenter: Tae-Dong Kim, PhD

Tae-Dong Kim, Ralf Janknecht

Department of Cell Biology, Oklahoma University Health Sciences Center

Histone modifications have crucial roles in epigenetic regulation. In particular, histone lysine methylation is important for transcriptional control during diverse biological processes. JMJD2A (also known as KDM4A) is a histone demethylase that removes methyl moieties from lysine 9 and lysine 36 on histone H3. Although recent observations have shown oncogenic activity of JMJD2A, little is known about its role in prostate cancer progression.

Here, we show that JMJD2A expression was highly elevated in human prostate cancer compared with normal tissue. To investigate whether JMJD2A is involved in prostate cancer development, we generated transgenic mice (TG) expressing JMJD2A under the probasin promoter that targets expression to prostate epithelium. JMJD2A TG mice displayed higher frequencies of mouse prostatic intraepithelial neoplasia (mPIN) than age-matched wild-type mice. A loss-of-function confirmed that JMJD2A promoted cell proliferation in LNCaP prostate cancer cells. JMJD2A increased MMP1 expression through binding to the proto-oncogene ETV1 which itself is involved in prostate tumorigenesis. Furthermore, we found two tumor associated target genes (YAP1 and PMEPA1) are significantly affected by Knockdown of JMJD2A and ETV1. These findings suggest that JMJD2A functions as an oncogene and plays a critical role in prostate cancer development.

IN VITRO AND IN VIVO EVALUATION OF ENZYME PRODRUG THERAPIES TARGETED TO BREAST CANCER VASCULATURE

Presenter: John Kraiss

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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, a protein with strong binding affinity for phosphatidylserine. Fusions with annexin I are also under development to examine the effect of different internalization properties. Three fusions have been developed using bacterial purine nucleoside phosphorylase (PNP), yeast cytosine deaminase (CD), or bacterial methionine- γ -lyase (MET). Our results compare the *in vitro* and *in vivo* effect of the three targeted systems.

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 fluorescence 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. Preliminary combinatory studies have been performed with docetaxel and rapamycin. Docetaxel has been shown to increase externalization of phosphatidylserine, enhancing the targeting of the enzymes to the tumor. Rapamycin exhibits an anti-angiogenic effect, hindering tumor regrowth.

In vitro results show successful binding and killing of breast cancer and endothelial cells representative of tumor vasculature. 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. Combinatory studies with docetaxel yielded mixed results, with a strong tumor suppressive effect with PNP and minimal effect with MET. Preliminary studies combining rapamycin with MET yielded a >80% reduction in tumor volume.

The MET enzyme prodrug system targeted with annexin V effectively inhibited growth of MDA-MB-231 cells in SCID mice and was more effective than PNP and CD systems. Combinatory treatments with docetaxel and rapamycin yielded promising results with the potential for significant tumor reduction.

EXCISE TAX AND PRICING DIFFERENTIALS AT TRIBAL SMOKE SHOPS IN OKLAHOMA: OPPORTUNITIES FOR HARMONIZATION

Presenter: Fritz L. Laux, PhD

Fritz L. Laux, Ph.D¹, Frank J. Chaloupka, Ph.D², Laura A. Beebe, Ph.D³,

¹Northeastern State University; ²University of Illinois at Chicago; ³University of Oklahoma

With a patchwork of tribal versus nontribal land ownership and no formal reservations, the nature and geography of tribal smoke-shop sales in Oklahoma is different than elsewhere in the United States. Furthermore, the excise tax rate charged by the state for cigarette sales varies from tribe to tribe and has taken 5 distinct levels, ranging from 5.75 cents to \$1.03 per pack. There has recently been significant flux in the tax treatment of Oklahoma cigarettes, with active renegotiation of tribe-state tax treaties among Oklahoma's 38 federally recognized tribes.

We conducted two waves of site visits to nearly all smoke shops in the northeastern quarter of the state, an area containing the City of Tulsa and 60 percent of all tribal outlets. We recorded representative prices, looked for the sale of illegal (tax-free) cigarettes, and verified the tax rate paid (via tax stamp) for each shop. For each tribal outlet visited, we also collected price data for a nearby nontribal outlet (when practical). One wave of price data for shops in the rest of the state was obtained via phone survey. We supplemented these field data with archival information on tax revenue collections and state-tribal tax treaties.

We found that lowest-taxed cigarettes, mostly sold in the far northeastern corner of the state, tended to be priced at discounts that were even greater than the differential in tax rates. This suggests that price competition between the outlets of the low-taxed tribes, particularly in the Miami area, has been especially strong. Measuring the impact of changes in tax rates and the elimination of untaxed cigarette sales by one of the state's major tribes, that's located near Tulsa, we found that it had little effect on pricing or sales volume for the nearby smoke shops of a neighboring tribe. This suggests that inter-tribal price competition for cigarette sales in areas outside of the state's northeast corner has been less of a factor than competition from nontribal retailers. The implications are that low-taxed outlets would benefit from coordinated price increases, as could potentially be arranged via cooperative treaty arrangements. For the rest of the state, although a coordination of price increases across tribes would be beneficial, it seems that tribes have more latitude for increasing tribal revenue collections via unilateral changes in tribal cigarette taxation and pricing policies.

EFFECTS OF DURATION OF ELECTRONIC CIGARETTE USE

Presenter: William V. Lechner

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Aims: To examine the effects of duration of e-cigarette use on several factors including current tobacco cigarette use, dependence to e-cigarettes, frequency of e-cigarette use, and the strength of nicotine solution used in e-cigarettes.

Background: Sales, awareness, and public debate regarding electronic cigarette (e-cigarette) use have increased sharply and steadily since their advent in 2003. E-cigarettes, which deliver nicotine through inhaled vapor, have been viewed as both a threat and a potential benefit to public health. Despite great strides made in researching these products over the last several years, many questions remain unanswered, including questions regarding the effects of e-cigarette use over time.

Design and setting: Individuals were recruited at e-cigarette retail locations in a large metropolitan city in the Midwestern U.S. in July, 2013. One-hundred and fifty-nine participants with a mean age of 35.8, 84.8% Caucasian, 53.7% male completed a brief (29 item) self-report measure assessing behaviors and perceptions regarding e-cigarette and traditional cigarette use as well as demographic information.

Findings: Increased duration of use was associated with decreased current cigarette use. Additionally, past heavy smokers (i.e. ≥ 10 cigarettes per day) and past light smokers demonstrated significantly different patterns of dependence with duration of use. Overall, e-cigarette users decreased the strength of nicotine in their e-cigarette products. Duration of use was not associated with changes in strength of nicotine, as some decreased nicotine strength very quickly while others took much longer. Frequency of e-cigarette use increased with increasing duration of use; however, this finding was not significant when traditional cigarette use was added as a covariate.

Conclusions: Duration of e-cigarette use appears to be associated with decreased cigarette use and differing patterns of dependence contingent on past smoking history. Additionally, reported frequency of e-cigarette use increased with increasing duration of use. However, post-hoc analyses revealed that this is likely a function of individuals transitioning from traditional cigarettes to e-cigarettes over time.

FORMULATION AND CHARACTERIZATION OF AN ULTRASOUND IMAGEABLE LOW TEMPERATURE SENSITIVE LIPOSOME FOR IMAGE GUIDED DRUG DELIVERY

Presenter: Danny Maples

Danny Maples, Ryan Newhardt, and Ashish Ranjan
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Current nanocarrier-based solid tumor chemotherapy is limited by low intratumoral drug release rates, heterogeneous distribution, and lack of an accurate means to implement control of real-time drug delivery. To address these critical limitations, the objective of this study was to develop a heat-activated liposome encapsulating an echogenic ultrasound contrast agent (E-LTSL) that permits real-time *in vivo* tracking and locally inducible drug release in combination with High Intensity Focused Ultrasound (HIFU).

E-LTSL was passively loaded with perfluoropentane (PFP)/1,3-propanediol (PD) contrast agent emulsion and actively loaded with antitumor agent doxorubicin (Dox). E-LTSL was characterized for size, encapsulation efficiency and its ability to encapsulate PFP/PD emulsion by TEM. Doxorubicin release and imageability from the optimized E-LTSL formulation was also examined in tissue-mimicking phantoms to ease preclinical translation.

Synthesized E-LTSL was 144.1 nm in diameter, and Dox encapsulation was 60-70%. TEM studies showed that E-LTSL effectively emulsifies PFP within the liposome core, and that the co-encapsulation of PFP in E-LTSL had no effect on Dox release as a function of temperature. Incubation at 37°C for >20 minutes in the presence of continuous-wave focused ultrasound (3-12 MHz), vs. its release from conventional LTSL phantom study demonstrated a progressive contrast enhancement with increased temperature, thereby confirming the imageability of our carrier. Our data suggests that E-LTSL can allow real-time control of image-guided drug delivery (IGDD) in combination with HIFU.

NECROSIS-INITIATED COMPLEMENT ACTIVATION LEADS TO PROLIFERATION IN MEDULLOBLASTOMA CELLS IN VITRO

Presenter: Adrian J Maurer

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Complement plays an important role in the immune response to pathogens and inflammation, and necrosis is a well-known initiator of the cascade. Effector molecules (C3a and C5a) have been implicated in the stimulation of progenitor cells for repair and regeneration of damaged CNS tissue. Necrosis is a prognostic indicator on histologic examination of medulloblastoma, predicting poorer outcomes. We sought to investigate the role of complement activated by necrosis in proliferation of medulloblastoma cells.

Immunohistochemistry using iC3b antibody and H&E staining was performed on adjacent sections of medulloblastoma specimens, which displayed activated complement antibody staining in corresponding regions of necrosis. Western blot was performed on wild type, Daoy, D283, and D341 lines for C3a receptor (C3aR) demonstrating that medulloblastoma cells express this receptor protein on the cell surface. Knockdown assays using siRNA for C3aR were performed and growth curves were attained, revealing statistically significant reduction in proliferation of 35.7% at 72 hours ($p=.001$). Western blots were performed on these assays, demonstrating knockdown of C3aR at 72 hours.

Medulloblastoma cells express C3aR, and respond to necrosis-induced activation of the C3a effector molecule by proliferating. While the role of complement has been attributed to inflammation and immune response to pathogens, ours and other recent data suggests the system has broader functions, including a possible role of the C3a molecule as a proliferation signal through C3aR. The siRNA-mediated knockdown of C3aR inhibits proliferation of these cells, and may be a promising target for subsequent developments of medulloblastoma therapies.

AZD2281, A PARP INHIBITOR, ENHANCES THE RESPONSE OF HUMAN BREAST CANCER CELLS TO IONIZING RADIATION BY SUPPRESSING DNA REPAIR

Presenter: Meghna Mehta

Meghna Mehta¹, Rajagopal Ramesh^{2,3}, Terence Herman^{1,3}, Anupama Munshi^{1,3}

Departments of ¹Radiation Oncology and ²Pathology, ³Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center

Poly (ADP-ribose) polymerase (PARP-1), a member of the PARP family of enzymes, is a nuclear protein that modulates the cellular response to DNA damage. PARP-1 gets activated in response to metabolic, chemical or radiation induced DNA single strand breaks in the cells. The enzyme cleaves nicotinamide adenine dinucleotide into branched polymers of ADP-ribose which are transferred to a set of nuclear proteins causing chromatin relaxation and recruitment of other repair proteins into the damaged site and hence maintains cell's genomic integrity. Since PARP-1 plays a critical role in DNA repair process, inhibition of PARP is an attractive strategy to sensitize cells to DNA-damaging agents such as platinum based drugs, temozolomide and ionizing radiation. A number of highly potent and specific PARP inhibitors are currently under clinical trials for use in treatment of cancer. AZD-2281(Olaparib) is a novel, small molecule, orally bioavailable inhibitor of PARP-1 and PARP-2 that induces synthetic lethality in homologous recombination-deficient cells such as those with homozygous BRCA mutations. The purpose of this study was to investigate the ability of AZD2281 to radiosensitize human breast cancer cells- MCF-7, MDA-MB-231 and Hs578t. Cells were treated either with vehicle alone or with AZD2281 (4 μ M for 24 hrs for MCF-7 and 2 μ M for 24hrs for the MDA-MB-231 and Hs578t) in combination with radiation. Clonogenic cell survival assay showed that AZD2281 enhanced tumor cell radiosensitivity with the survival factor at 2Gy (SF2) being reduced from 26%, 52.8%, and 51.5% in vehicle treated to 18.5%, 27.8%, and 45.52% in AZD2281-treated MCF-7, MDA-MB-231, and Hs578t cells respectively. Cell cycle analysis revealed that AZD2281 alone and in combination with radiation had a strong effect on cell cycle arrest at G2/M phase and a decrease in G1 phase in all the three cell lines. Molecular studies revealed AZD2281-mediated radiosensitization involved the DNA repair pathway as evidenced by the reduction in the expression of repair proteins, Ku70 and Ku80 and prolonged expression of phosphorylated γ -H2AX. Senescence β -galactosidase staining showed that cells treated with AZD2281 and radiation had accelerated senescence. These results indicate that AZD2281 enhances tumor radioresponse by inducing senescence and inhibiting DNA repair after exposure to radiation.

SMOKELESS TOBACCO USE AMONG COLLEGE STUDENTS AFTER A CAMPUS-WIDE TOBACCO BAN

Presenter: Ellen Meier

Ellen Meier^{1,2}, M.S., William V. Lechner^{1,2}, M.S., Mary Beth Miller¹, M.S., Josh L. Wiener³, Ph.D.

Approximately 45.3% of tobacco users fall between the ages of 18 and 25 years, identifying college students as an at-risk group for SLT use (CDC, 2009; Morrell, Cohen, Bacchi, & West, 2005). The American College Health Association's (ACHA) has set the goal to create smoke-free college campuses (ACHA, 2009) by 2020. Campus-wide interventions aimed at reducing smoking prevalence have shown to be effective (Lechner, Meier, Miller, Wiener, & Fils-Aime, 2012). However, research examining the effects of these interventions on SLT use is scarce (Murphy-Hoefer et al., 2005).

The current study examined the effectiveness of a campus-wide anti-tobacco intervention at decreasing prevalence of SLT use over a four year period. Undergraduate students ($N = 2,293$) enrolled at a large southern plains university between 2007 and 2010 completed a self-report measure assessing demographics and tobacco use behaviors. Surveys were administered at four time points including baseline and during mid-fall semester over the following three years. Logistic regressions analyzing assessment year as a predictor of SLT use revealed that overall rates of SLT use displayed a significant decline from 23.2% at baseline to 15.1%, 14.2%, and finally 16.4% over the four assessment years. Participants in 2008 were less likely to report using SLT as compared to participants in 2007 (OR = .549) and this trend continued in 2009 (OR = .561) and 2010 (OR = .728). Among on-campus residents, rates of SLT use decreased from 14.9% at baseline to 7.7%, 9.3%, and 6.4% during successive years; however, this decreased trend of tobacco use rates was not significantly lower until 2010 (OR = .358).

Fraternity residents displayed an initial significant decrease from 31.6%, to 12.8%, 15.5%, but rebounded to 21.6% in 2010. Compared to baseline, SLT use was significant lower in 2008 (OR = .269) and 2009 (OR = .378). However, in 2010 the proportion of participants who reported SLT use did not differ from 2007 (OR = .707). Similarly, off-campus residents displayed an initial significant decrease from 24.7% to 17.3% and 16.3%, but a rebound during the last assessment year (23.9%). SLT use was significantly lower in both 2008 (OR = .618) and 2009 (OR = .604). However, in 2010 the proportion of participants who reported SLT use did not differ from 2007 (OR = .956).

A campus-wide tobacco intervention appears to be an effective method for reducing smokeless tobacco rates among college students. However, it appears as though certain high-risk groups, such as those residing in fraternities or off-campus housing, are more resistant to this type of intervention. Further research is needed to examine the mechanisms leading to a collapse in the effectiveness of campus-wide interventions within these groups.

PROTEIN KINASE C ACTIVATION RAPIDLY DOWN-REGULATES OATP1B3 TRANSPORT FUNCTION IN PRIMARY HUMAN HEPATOCYTES

Presenter: Xiaojie Meng

Xiaojie Meng¹, Kathleen Köck², Jun Li², Kim L. R. Brouwer² and Wei Yue¹

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Purpose: The organic anion transporting polypeptide (OATP) 1B3 is a liver-specific protein that transports many drugs and endogenous compounds. Limited information exists regarding regulation of OATP1B3 function. OATP1B3 is a putative phosphoprotein with consensus phosphorylation sites for protein kinase C (PKC). The purpose of this study was to characterize the effect of PKC activation on the transport kinetics of OATP1B3 using the specific OATP1B3 substrate CCK-8 as a probe, and to elucidate potential mechanism(s) for such regulation.

Methods: Human sandwich-cultured hepatocytes (SCH) were pre-treated with the PKC activator phorbol-12-myristate-13-acetate (PMA), the PKC inhibitor bisindolylmaleimide (BIM) I, or BIM I prior to PMA treatment. Accumulation of [³H]CCK-8 (1 μM, 3 min) in SCH was compared between treatments and control. CCK-8 transport kinetics (K_m and V_{max}) in control and PMA-treated SCHH was estimated by nonlinear least squares regression using WinNonlin (Pharsight Corporation).

Results: PMA pre-treatment significantly decreased CCK-8 accumulation in SCH. Treatment with the PKC inhibitor BIM I (1 μM, 20 min) prior to PMA treatment blocked this effect, indicating that PKC activation is involved in the PMA-induced down-regulation of OATP1B3 transport function. The V_{max} values for CCK-8 transport in SCHH were not affected by PMA pre-treatment; however, the K_m values for CCK-8 were significantly increased in PMA-pre-treated SCHH ($12.5 \pm 2.6 \mu\text{M}$ vs. $44.5 \pm 9.3 \mu\text{M}$ in control and PMA-pretreated cells, respectively; mean \pm S.E., n=3 livers). Decreased CCK-8 uptake occurred as early as 10 min following PMA pre-treatment, suggesting a rapid down-regulation of OATP1B3 function. Without any pre-treatment, PMA did not affect CCK-8 uptake, suggesting the PMA-induced down-regulation of OATP1B3 transport function is not due to direct inhibition by PMA.

Conclusions: PKC activation in SCHH increased the K_m characterizing CCK-8 transport, indicating a decreased substrate affinity towards OATP1B3. PKC activation rapidly down-regulated OATP1B3 transport function in an indirect manner. These studies provide a novel mechanism for impaired hepatic uptake of OATP1B3 substrates by kinase modulator(s).

OVEREXPRESSION AND PURIFICATION OF AFFINITY TAGGED HUMAN JMJD4 FOR STRUCTURAL STUDIES

Presenter: Blaine Mooers, PhD

Chiedza Kanyumbu, Irene Chen, Kyle Cahill, Molly Denny, and Blaine Mooers
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Jumonji domain-containing protein 4 (JMJD4) belongs to the Jumonji C (JmjC) family of proteins. Members of this family have been shown to have demethylase activity on the methyllysines located along the N-terminal tails of histones. The state of methylation of these lysines is associated with gene regulation and, consequently, diseases including several cancers. Because members of the JmjC family have been linked to several cancers, structural data from these proteins can be used in structure-based drug design and development.

To date, no three-dimensional structural data on JMJD4 are available. However, phylogenetic analyses by us and others show that JMJD4 is more similar to JMJD5 and JMJD6 than to the other known lysine demethylases, so further experimental characterization of JMJD4 promises to reveal that JMJD4 has a function that is unique in the JmjC family. Our immediate objective is to obtain sufficient quantities of pure JMJD4 for structural studies in solution by small angle X-ray scattering (SAXS) and in crystals by X-ray diffraction.

Previous work with a GST-JMJD4 isoform 1 fusion produced milligram quantities of protein, a small fraction of which was soluble but formed aggregates and did not readily yield crystals. We used homology modeling to guide the design of several maltose binding protein (MBP)-JMJD4 constructs of isoform 2 of JMJD4 that produced higher yields of soluble fusion protein with no protein aggregation (verified by size exclusion chromatography and dynamic light scattering analysis). Our present efforts are focused on optimizing SAXS and crystallization conditions as well as making the corresponding fusion constructs of isoform 1 of JMJD4 for comparative studies.

TUMOR-TARGETED NANOPARTICLE DELIVERY OF HuR-RNAi SUPPRESSES LUNG CANCER CELL PROLIFERATION AND CELL MIGRATION

Presenter: Ranganayaki Muralidharan

Ranganayaki Muralidharan^{1,3}, Anish Babu^{1,3}, Kanthesh Basalingappa^{2,3}, Anupama Munshi^{2,3}, Rajagopal Ramesh^{1,3}.

Departments of ¹Pathology and ²Radiation Oncology, ³Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Objective. HuR is an mRNA-binding protein that regulates mRNAs of several oncoproteins by increasing mRNA stability and translation. HuR overexpression is a poor prognostic marker in a spectrum of human cancers and correlate with drug resistance. In the present study we tested *in vitro* the efficacy of a nanoparticle (NP) containing HuR-specific siRNA and targeted towards folate receptor (Fr) overexpressing lung cancer cells.

Methods. Tumor targeted nanoparticle containing scrambled (control) siRNA or HuR-specific siRNA (100 nm) was synthesized and decorated with DSPE-PEG5000-folate and labeled as C-FNP and HuR-FNP respectively. Transfection efficiency, cell viability, cell migration and HuR knock down studies were performed using human lung cancer (H1299, A549) and normal fibroblast (MRC-9) cell lines.

Results. HuR protein expression in H1299 and A549 was higher than in MRC-9 cell line. Folate receptor (Fr) expression was higher in H1299 than in MRC9. Fr expression was not detected in A549 cells. Transfection efficiency study showed FNP uptake was highest in H1299 cells with lowest uptake by A549 cells. A significant reduction in cell viability was observed in HuR-FNP-treated H1299 cells compared to C-FNP-treatment and correlated with a marked reduction in HuR mRNA and protein expression levels. Analysis for proteins (Bcl2, Cyclin D1, HIF-1 α) whose mRNAs are targets for and regulated by HuR showed diminished expression in HuR-FNP-treated cells. Finally, cell migration was significantly inhibited in HuR-FNP-treated H1299 cells compared to C-FNP treatment.

Conclusions. Our study results demonstrated tumor-targeted nanoparticle delivery of HuR-RNAi suppresses lung cancer cell proliferation and cell migration.

BMI-1 REGULATES BIOENERGETICS IN OVARIAN CANCER

Presenter: Soumyajit Banerjee Mustafi

Soumyajit Banerjee Mustafi¹, Priyabrata Mukherjee², and Resham Bhattacharya³

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Ovarian Cancer is a leading cause of gynecological cancer death with more than 14000 death each year in US. However the treatment options are limited with low relative five-year survival rate and platinum drug resistance to chemotherapy is a common occurrence. Bmi-1, a member of the polycomb complex 1 is a known transcriptional repressor and mediates gene silencing by modification and/or alteration of the chromatin structure. It is of immense importance to evaluate the role of Bmi-1 at the cellular and molecular level that promotes metastasis, chemotherapy resistance and angiogenesis, all of which present a significant barrier to effective therapy. Enhanced metabolic demand is a key feature of cancer cells and hence interfering with the metabolism can provide a potentially effective strategy to selectively target ovarian cancer cells.

We previously demonstrated that Bmi-1 knockdown induced ROS (reactive oxygen species) in ovarian cancer (OVCa) which encouraged us to put forward the hypothesis that Bmi-1 might have a direct or indirect role in regulating mitochondrial function and metabolism. Surprisingly, cellular fractionation and biochemical studies revealed that Bmi-1, which was previously reported to be predominantly nuclear, was also present in significant amount in the mitochondria of A2780 and CP20 OVCa cells but not in the normal immortalized ovarian surface epithelial (OSE) cells. Ectopically expressed Bmi-1 also localized to the nucleus and in the mitochondria in OSE cells that otherwise express low levels of Bmi-1 compared to OVCa cells. Therefore we studied the effects of Bmi-1 on mitochondrial function and cellular bioenergetics. Bmi-1 knock down (Bmi-1 KD) in CP20 cells and evaluation of the mitochondrial function in terms of oxygen consumption rate (OCR) showed significantly reduced basal respiration. Further treatment with the pharmacological uncoupler FCCP which lowers mitochondrial membrane potential and enhances electron transport chain (ETC) flux markedly reduced OCR in the Bmi-1 KD cells. Extracellular acidification rate (ECAR) was significantly higher in the Bmi-1 expressing cells compared to the KD cells during the basal respiration state indicating enhanced glucose dependence in the CP20 cells. Compared to control, Bmi KD CP20 cells demonstrated enhanced glucose sensitivity and reduced growth rate in a dose dependent manner at lower glucose concentrations supporting the hypothesis that Bmi-1 is an important regulator of mitochondrial function and modifying the glycolytic phenotype in ovarian cancer represents a selective growth advantage. Bmi-1 KD in CP20 cells decreased their resistance to cisplatin and showed significantly lower viability in response to topotecan. Our data for the first time revealed the mitochondrial localization and a role for Bmi-1 in glycolytic shift of OVCa cells. This warrants further in vivo studies using Bmi-1 as a potential therapeutic target in combination with drugs that perturb glucose metabolism, to effectively treat Ovarian Cancer.

MODULATORS OF ETV1 IN PROSTATE TUMORIGENESIS

Presenter: Sangphil Oh

Sangphil Oh and Ralf Janknecht

Department of Cell Biology, University of Oklahoma Health Sciences Center

Although the ETS transcription factor and oncoprotein ETV1 is overexpressed in many prostate cancer patients, ETV1 transgenic mice only develop PIN, a precursor of prostate cancer, but not adenocarcinomas. This lack of full tumor development in the mouse model led us to seek relevant signaling pathways and/or modulators that can inhibit/promote transcriptional activity of ETV1 in prostate tumorigenesis. Here we found that non- σ 14-3-3 proteins, but not the 14-3-3 σ tumor suppressor, can bind to ETV1 in a manner dependent on S216 phosphorylation and synergize with ETV1 to increase invasion and proliferation of prostate cells. Further, we found that Smad proteins compete with 14-3-3 proteins for ETV1 interaction and inhibit ETV1's transcriptional activity. In line with this, downregulation of Smad3 stimulated prostate cancer cell invasion, whereas downregulation of ETV1 suppressed the ability of Smad3 shRNA to increase cell invasion, suggesting that Smad3 exerts its effects through ETV1. Similarly, Smad4 downregulation increased anchorage-independent growth of prostate cancer cells, while downregulation of both ETV1 and Smad4 did not. Finally, we show that Smad mRNAs are mostly downregulated in ETV1-positive prostate tumors, suggesting that the TGF- β signaling pathway restrains ETV1-dependent cell functions, including anchorage-independent growth, invasion and possibly growth, through Smad proteins.

REGULATION OF ORGANIC ANION TRANSPORT POLYPEPTIDES BY TYROSINE KINASE INHIBITORS

Presenter: Sonia Pahwa

Sonia Pahwa, John Powell and Wei Yue

Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma Health Sciences Center

Purpose: Organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 are hepatic membrane transport proteins that mediate uptake of many drugs (*e.g.*, statins) and endogenous compounds into the liver. *In silico* prediction suggests that OATP1B1 and OATP1B3 are putative phosphorylated proteins. Many tyrosine kinase inhibitors (*e.g.*, erlotinib) have been developed for targeted cancer therapy. The purpose of this study was to characterize phosphorylation status of OATP1B1 and OATP1B3 and to elucidate the impact of TKIs on OATP1B1- and OATP1B3-mediated substrate transport in human sandwich-cultured hepatocytes (SCH) and transporter-overexpressing cell lines.

Methods: To determine the phosphorylation status of OATP1B1, Flag-tagged OATP1B1 was immunoprecipitated from HEK293-OATP1B1 followed by immunoblot with anti-phospho-Ser/Thr/Tyr, anti-phospho-Ser/Thr, and anti-phospho-Tyr antibodies. Direct drug interactions between erlotinib (0.3 μ M and 10 μ M) and rosuvastatin (5 μ M, 5 min) were determined in human SCH. To determine mechanism-based interaction between TKIs and OATP substrates, HEK293 or HeLa cells were transfected with OATP1B1 or OATP1B3 and treated with TKIs for designated times. Accumulation of [³H]E217G and [³H]CCK-8 (1 μ M, 3 min) was compared between TKI-treatment and vehicle control in OATP1B1 and OATP1B3-transfected cells, respectively.

Results: Flag-tagged OATP1B1 was specifically immunoprecipitated with Flag antibody. Immunoblot with anti-phospho-Ser/Thr/Tyr antibody indicated that OATP1B1 is a phosphorylated protein. Immunoblot with anti-phospho-Ser/Thr and anti-phospho-Tyr antibodies further characterized that OATP1B1 is a tyrosin-phosphorylated protein. No phosphorylation signals were detected when immunoprecipitated with negative control normal IgG. Erlotinib did not directly affect rosuvastatin uptake in SCH. However, pre-treatment with TKIs decreased substrate accumulation in HeLa cells and HEK293 cells transfected with OATP1B1 or OATP1B3.

Conclusions: This is the first indication that OATP1B1 is a tyrosin-phosphorylated protein, which provides rationale for a mechanism-based interaction between TKIs and OATP. Although without pre-treatment, there is no direct interaction between TKIs and OATP substrate rosuvastatin, our data support that a mechanism-based interaction between TKIs and OATP may exist, resulting in altered transport of OATP1B1 and OATP1B3 substrates presumably by modulating phosphorylation status of OATP. These studies will help us to provide a mechanistic model to study drug-drug interactions between TKIs and OATP substrates.

NEEM LEAF EXTRACT, RICH IN *NIMBOLIDE* AND *AZADIRACHTIN* TARGETS RADIATION-INDUCED STEMNESS IN SURVIVING BREAST CANCER CELLS

Presenter: Vijayabaskar Pandian, PhD

Vijayabaskar Pandian¹, Mohan Natarajan², Terence S. Herman¹, Natarajan Aravindan¹

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Recently, we have shown that the neem leaf extract (NLE) rich in *Nimbolide* and *Azadirachtin* exerted radiosensitization and alleviates tumor progression in varied solid tumor models. Accordingly, in this study, we investigated its potential in the regulation of radiation (IR)-induced stemness in surviving breast cancer (BCa) cells. Human breast adenocarcinoma (MCF-7) cells either mock-irradiated or exposed to IR (2Gy) with or without NLE (1, 10 or 100µg) pre-treatment (for 3h) and analyzed at 3h or 24h post-IR. Transcriptional alterations of 93 molecules that drive EMT, CSCs self-renewal capacity and pluripotency maintenance were analyzed using QPCR profiling. NANOG, SOX2, and N-cadherin expression was examined by immunoblotting. Radiation profoundly increased 65 stem-cell related molecules in surviving BCa cells. NLE exerted a dose-dependent (1µg, 21; 10g, 49; 100µg, 62 genes) inhibition of IR-induced stem-cell related molecules. Second-phase observations at 24h post-IR revealed no recovery of NLE-inhibited transcription with complete inhibition of 12, 63 and 62 genes after 1, 10 and 100µg. Gene comparison analysis revealed both '*dose-independent*' (21genes at 3h and 12genes at 24h) and '*time-independent*' (6, 50 and 61 genes at 1µg, 10µg and 100µg respectively) inhibition. Interestingly, six genes (*BMP4*, *CDH1*, *EGF3*, *FOXA2*, *GSK3β* and *HDAC2*) showed both '*time-and-dose-independent*' inhibition. Coherently, immunoblotting revealed a consistent regulation of IR-induced NANOG, SOX2, and N-cadherin in the surviving BCa cells. Together these data demonstrate that NLE targets IR-induced stemness in surviving BCa cells and may thus serve as a potential "deliverable" to negate breast cancer relapse and progression.

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

Presenter: Janani Panneerselvam, PhD

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The stromal derived factor (SDF)-1/chemokine receptor (CXCR)-4 signaling has been shown to contribute in the growth and metastasis of non-small cell lung cancer (NSCLC). Suppressing the SDF-1/CXCR4 signaling axis is likely to reduce the incidence of tumor metastasis and thus is a target for lung cancer treatment. CXCR4 antagonist has been developed and is currently in clinical testing for lung cancer treatment. Early clinical results however have been disappointing and thus warranting new and more effective inhibitors of SDF-1/CXCR4 axis. In the present study we investigated the inhibitory effect and molecular mechanism by which interleukin-24 (IL-24), a novel tumor suppressor/cytokine blocked SDF-1/CXCR4 axis and suppressed lung cancer cell migration and invasion *in vitro*. Furthermore, combination therapy of IL-24 with AMD3100, an antagonist of CXCR4 was also investigated.

Analysis for endogenous CXCR4 expression in four (H1299, A549, H460, HCC827) lung cancer cell lines showed that the relative CXCR4 expression levels varied among the cell lines with the highest expression occurring in H1299 cells. Next, doxycycline-induced expression of exogenous IL-24 in H1299-IL24 cell line reduced CXCR4 mRNA levels indicating IL-24 inhibited CXCR4 at the transcriptional level. CXCR4 mRNA inhibition correlated with reduced phosphorylated and total CXCR4 protein expression. Analysis of proteins downstream of CXCR4 showed decreased expression of phosphorylated (p) Akt, pmTOR, pPRAS40 and HIF-1 α . Functional assays revealed IL-24 inhibited tumor cell migration and invasion in the presence of CXCR4 agonist, SDF-1. These results demonstrated IL-24 inhibited the CXCR4 signaling pathway. Finally, IL-24 when combined with AMD3100, an antagonist of CXCR4 greatly reduced pAKT and pPRAS40 expression that resulted in an enhanced inhibitory activity on H1299 cell migration.

Our study results provide evidence for the first time that IL-24 inhibits lung tumor cell migration and invasion by disrupting the SDF-1/CXCR4 signaling pathway and that IL-24 when combined with AMD3100 produced greater antimetastatic activity. Thus, combining IL-24 with inhibitors of the SDF-1/CXCR4 axis is an attractive therapeutic strategy for lung cancer metastasis.

DUAL-MODE IMAGEABLE LIPOSOME FOR SYNERGISTIC TUMOR TARGETING AND THERAPY

Presenter: Venkatesan Perumal

Venkatesan Perumal, Kevin McLean, and Ashish Ranjan
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Background/objective: Docetaxel (DTX) is currently the standard of care, first line treatment in castrate resistant prostate cancer (CRPC) despite its clinically significant toxicity for the patient. There is a critical need to develop a reliable encapsulation method that can limit side effects and enhance drug targeting of DTX. Objectives of this study were to: 1) formulate a library (D1, D2, D3 and D4) of DTX encapsulated Low Temperature Sensitive Liposomes (LTSLs) for thermal enhancement of chemotherapy, and 2) characterize mild hyperthermia (40-42 °C) mediated DTX release *in vitro*.

Method: LTSL's were prepared by thin-film dispersion method in presence of a water soluble surfactants (D1), Pluronic F127 (D2-LTSL), Brij S20 (D3-LTSL) and Brij S10 (D4-LTSL). D1, D2, D3 and D4 LTSLs were characterized for size, encapsulation and loading efficiency, and release in physiological buffer.

Results: The efficiency of DTX encapsulation (% w/w) in D1, D2, D3 and D4 LTSLs was ~74, 30, 85 and 47%, respectively and loading efficiency (% w/w) in D1, D2, D3 and D4 LTSLs was ~2.21, 0.87, 2.52 and 1.4%, respectively. DTX release analysis for all LTSLs are in progress. Addition LTSLs have displayed thermosensitivity (DTX release) at mild hyperthermia in the order of D1>D3>D4>D2. The encapsulation of DTX in LTSLs in the presence of a surfactant may ease pre-clinical translation for prostate cancer therapy.

CATHETER-RELATED COMPLICATIONS IN ACUTE MYELOID LEUKEMIA PATIENTS AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

Presenter: Namali Pierson, MD

Mohammad O. Khalil, MD¹, Namali Pierson, MD¹, George Selby, MD¹, Mohamad Cherry, MD¹, Jennifer Holter, MD¹

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Background: Intravenous catheters are widely used in hematopoietic stem cell transplant (HSCT) patients. Complications associated with these catheters are frequently encountered and contribute to morbidity, mortality, and increased cost of treatment. Studies investigating catheter-related complication rates in acute myeloid leukemia (AML) patients are limited. We retrospectively studied catheter complications in a AML patients after HSCT.

Methods: AML patients above the age of 18 who had HSCT at The University of Oklahoma Health Sciences Center between January, 2000 and June, 2012 were identified and medical records were reviewed. Statistical analysis was performed using SAS 9.2 software (SAS Institute Inc.). Fisher's exact test was used to compare patients in the different groups.

Results: Sixty two patients were included. 56 (93%) had Hickman, 30 (50%) PICC and 7 (12%) IP. Twenty eight patients had one catheter type only (24 Hickman and 4 PICC). BSI occurred in 37% of all cases. BSI rates according to the presence or absence of a particular catheter type were 38% vs. 33% for Hickman ($p=1.0$), 37% vs. 38% for PICC ($p=1.0$) and 43% vs. 36% for IP ($p=1.0$). In patients with only one catheter type, BSI rate was 38% for Hickman compared with 50% for PICC ($p=0.92$). BSI occurred in 40% of patients 50 years of age or younger and in 29% of those >50 years ($p=0.56$). Patients with DCB transplant had 63% BSI rate compared with 31% in the other transplant types ($p=0.059$). Gram-positive cocci were isolated in 57% and Gram-negative rods in 26% of all infections. DVT occurred in 26% of all cases. DVT rates according to the presence or absence of a particular catheter type were 27% vs. 25% for Hickman ($p=1.0$), 37% vs. 17% for PICC ($p=0.14$) and 14% vs. 29% for IP ($p=0.66$). In patients with only one catheter type, DVT rate was 17% for Hickman compared with 25% for PICC ($p=0.4$). DVT occurred in 18% of patients 50 years of age or younger and in 47% of those >50 years ($p=0.026$).

Conclusions: Among AML patients who underwent HSCT at our institution, we did not observe any significant differences in catheter-related complications according to catheter type. DVT rate was significantly higher in patients older than 50 years. There was a trend of higher infection rate with double cord blood transplant compared with other transplant types.

MEASURING TOBACCO-INDUCED DNA DAMAGE TO PREDICT CANCER SUSCEPTIBILITY IN DIVERSE POPULATIONS

Presenter: Lurdes Queimado, MD, PhD

Vengatesh Ganapathy¹, Wilbur K. Mills¹, Ilangoan Ramachandran¹, Jeremy Jinkins¹, Elangovan Thavathiru¹, Leslie Chandler², Dini Chissoe¹, Lancer Stephens¹ and Lurdes Queimado¹⁻⁵

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

Background: Head and neck cancers are mostly linked to tobacco use, and therefore are preventable. Carcinogens in tobacco smoke causes various types of DNA damage overwhelming the DNA damage repair capacity of cells and leading to the development of cancer. Tobacco-induced DNA damage is modulated by genetic and epigenetic factors, as well as life-style choices, and is likely to be a major determinant of the individual susceptibility to tobacco-induced cancer. However, due to technical limitations, only a few types of tobacco-induced DNA damage have been quantified in human samples, and no reliable biomarkers of tobacco-associated risk have been identified. We have developed a novel primer-anchored DNA damage detection assay (PADDA) to map and quantify *in vivo* DNA damage. PADDA has higher sensitivity than other DNA damage detection assays and is the only available assay able to reliably quantify *in vivo* overall levels of DNA damage.

Aims: (1) To standardize PADDA for the detection of tobacco-induced damage. (2) To define the levels of persistent DNA damage in the oral mucosa of smokers in distinct ethnic groups. (3) To determine if the levels of tobacco-induced DNA damage vary significantly between ethnic groups.

Methods: To standardize the assay for the detection of tobacco-induced damage, PADDA was used on a high-throughput setting to quantify DNA damage in oral cell lines exposed to diverse doses of tobacco-smoke. For population studies, DNA was extracted from epithelial cells collected by oral scrapings from two distinct ethnic groups: 60 Caucasians and 60 American Indians. DNA damage was mapped and quantified on the *p53* gene of non-smokers, smokers and former smokers. Saliva cotinine levels were determined and used to check smoking status. Data were analyzed by chi-square goodness of fit and exact non-parametric tests.

Results: PADDA detected a dose-dependent increase in DNA damage induced by tobacco-smoke. We observed significantly higher levels of DNA damage in current smokers than in former-smokers or never-smokers. Remarkably, we observed significant differences in levels of tobacco-induced DNA damage between the transcribed and non-transcribed DNA strands in the *p53* gene. Furthermore, our data suggest that in smokers the DNA damage persists preferentially in *p53* nucleotides that are hotspots for mutation in head and neck cancer. Our preliminary results also pinpoint towards important differences in the steady-state levels of DNA damage in diverse ethnic groups.

Conclusion: PADDA detects an *in vitro* dose-dependent DNA damage in response to increased levels of tobacco-smoke. This is a crucial test of PADDA's accuracy and a prerequisite for its use in biomonitoring. PADDA documents the extent of tobacco-induced DNA damage *in vivo*, and reinforces the importance of smoking cessation. Of potential clinical importance, we show that the levels of tobacco-induced DNA damage vary between diverse ethnic groups. Application of this assay to large series of smokers and former smokers has a major potential to establish biomarkers of susceptibility to tobacco-induced disease, which can guide preventive and diagnostic strategies.

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

Wnt INHIBITORY FACTOR 1 IS DOWNREGULATED IN ADENOID CYSTIC CARCINOMA (ACC) AND ITS RE-EXPRESSION SUPPRESSES THE GROWTH OF ACC CELLS

Presenter: Ilangovan Ramachandran, PhD

Ilangovan Ramachandran¹, Liu Cheng² and Lurdes Queimado^{1,3-6}

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

Background: Adenoid cystic carcinoma (ACC) is the second most common salivary gland malignancy and the single most common malignancy in the submandibular gland. It is characterized by relentless course with multiple late local recurrences and distant metastasis, which are the overwhelming cause of mortality. The 5-year survival is about 60-75%, while the 10-year survival is only 30-54%. Aberrant activation of the Wingless-type (Wnt)/ β -catenin pathway contributes to various human tumors. Here, we report that Wnt inhibitory factor 1 (WIF1), a Wnt antagonist, is downregulated in ACC and its re-expression in ACC cells inhibit the cancer cell growth by diverse mechanisms.

Aims: 1) To assess the expression level of WIF1 protein in normal and ACC salivary gland samples, 2) to determine the mechanism of WIF1 down-regulation in ACC cells and 3) to delineate the effects of WIF1 re-expression on cell growth, migration, colony formation and senescence in ACC cells.

Methods: WIF1 protein expression was studied by immunostaining in the human normal and ACC salivary gland samples. Genomic DNA was isolated from ACC cell lines (ACC52 and ACC112) and processed for bisulfite modification to perform methylation-specific PCR. ACC52 and ACC112 cells were treated with 50 μ M of 5-aza-2'-deoxycytidine (DAC) for 4 days, and used for total RNA isolation and further real-time RT-PCR to determine *WIF1* mRNA expression. Transient transfection studies were performed to study the effects of WIF1 re-expression in ACC52 and ACC112 cells. Cell proliferation, migration and spheroid formation were determined by hexosaminidase assay, scratch assay and soft agar assay, respectively at different time points. To determine the effects of WIF1 on senescence, cells were transfected with WIF1 for 48 h and stained for senescence associated β -galactosidase.

Results: Immunostaining data demonstrated that WIF1 is downregulated in ACC compared with normal tissue. Methylation-specific PCR suggested that *WIF1* is hypermethylated in ACC cells. Treatment with the demethylating agent (DAC) resulted in restoration of *WIF1* mRNA expression in both the ACC cell lines studied. In addition, we also observed a significant decrease in cell number and an increase in cellular differentiation. Re-expression of WIF1 decreased the cell proliferation, migration and spheroid formation in ACC cells. Interestingly, WIF1 significantly increased the number of cells positive for senescence associated β -galactosidase in ACC52 and ACC112 cells.

Conclusions: Our findings suggest that WIF1 is downregulated in ACC. Promoter hypermethylation appears to be an important mechanism for WIF1 silencing in ACC cells. The tumor suppressive effects of WIF1 in ACC cells were caused by the inhibition of cell proliferation, migration, colony formation, and induction of senescence. Thus, our study emphasize the potential tumor suppressive role of WIF1 in ACC.

Grant support: This work was supported by the Adenoid Cystic Carcinoma Research Foundation (LQ). LQ holds a Presbyterian Health Foundation Endowed Chair in Otorhinolaryngology.

EF24 TARGETS RADIATION-INDUCED NFκB-DEPENDENT STEMNESS IN TRIPLE NEGATIVE BREAST CANCER CELLS

Presenter: Satish Kumar Ramraj

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Prognosis of patients with late stage BCa still remains poor, mostly due to development of chemoradioresistance followed by tumor recurrence. Cancer stem cells (CSCs), with higher drug efflux capability, and other stem cell-like properties were proposed to be responsible for resistance, relapse and progression of BCa. We have shown that EF24 alleviates radiation (IR)-orchestrated NFκB mediated clonal expansion. Herein, we investigated the potential of EF24 in the regulation of IR-induced NFκB dependent stemness in triple negative breast cancer cells (TNBC). MDA-MB-231 cells exposed to mock-IR or IR (2Gy) with/without EF24 were examined for transcriptional alterations of 93 EMT, CSCs self-renewal, pluripotency maintenance and other stem cell markers. NFκB (p50/p65) overexpression (with or without EF24) and RelA siRNA knockout (with IR) approach were used to delineate the role of IR-induced NFκB and the selective NFκB targeting of EF24 in this setting. Nanog, Sox-2, ABCG-2, N-Cadherin, POU5F1 and Myc expression was examined with immunoblotting. IR profoundly increased the transactivation of 86 stem-cell related molecules in TNBCs that are involved in cell survival. Interestingly, muting IR-induced NFκB attenuated 85 of those genes. Notably, EF24 suppressed identical 85 genes reproducing the inhibitory signature of NFκB muting. Coherently, activating NFκB induced 87 stem-cell related molecules in TNBC and of which 86 genes were completely suppressed with EF24. Alterations in the cellular expression levels of Nanog, Sox-2, ABCG-2, N-Cadherin, POU5F1 and Myc validates the potential of EF24 in mitigating IR-induced stemness in TNBC. Together these data demonstrates, at least in TNBC cells, IR-induced NFκB mediates increased stem-like characteristics and further imply that EF24 may alleviate stemness by selectively targeting IR-induced NFκB.

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

Presenter: Carol Rogers, PhD, RN

Carol Rogers, PhD RN and Melissa Craft PhD APRN-CNS AOCN
Assistant Professor OUCN

Background: Early recognition and aggressive therapies have raised survivorship rates among women with breast cancer. However, many survivors experience decreased quality of life (QOL) due to symptoms of fatigue and disturbed sleep that continue long after treatment. Exercise, meditation, and expressive writing (EW) have been effective in reducing fatigue among breast cancer patients. Sign Chi Do (SCD), a novel low-intensity exercise incorporates diaphragmatic breathing, meditation, gentle movement choreographed to a group of sign gestures, has shown improved function, endurance, and physical activity among sedentary older adults. EW is postulated to enhance SCD, make it more enjoyable, increase adherence to weekly practice, improve sleep, mood, QOL, and fatigue in breast cancer patients during treatment. Specific words chosen to write about could influence the benefit from this intervention.

Aims: To assess the choice of words used to write about for the EW component of the study and burden/benefit of an adapted SCD/EW intervention among a group of breast cancer survivors who have completed treatment.

Methods: A qualitative approach was used to study 4 breast cancer survivors post-treatment receiving a 6 week home-based SCD/EW class followed by a 6 week face-to-face class. A different group of words was practiced each week. After 6 weeks, participants were asked to write about the word grouping that was the most meaningful to them. Post intervention data included an analysis of the EW completed by participants, class instructor field notes, exit surveys, and focus group discussion related to the acceptance, feasibility and impact of adding the EW component to the SCD intervention.

Results: Participants were divided on the benefit of writing, which words were used and timing of the EW intervention. Half of the participants wrote about the Healthy, Happy, holy. One participant wrote about Peaceful Playful Present and one chose negative words Angry Anxious Absent to write about. Participants felt that the use of EW was helpful to them and felt that it made the home practice of SCD more meaningful however they were unsure whether the writing occurred at the right time.

Discussion and Conclusions: A specifically-adapted SCD, with meditation enhanced by EW, may be both feasible and acceptable to breast cancer survivors during treatment. The timing of the EW component and the synergistic nature of the intervention warrants further exploration. This SCD/EW intervention holds potential to impact the long term QOL of breast cancer patients in a variety of urban and rural settings.

COMMUNITY SUPPORT FOR LOCAL TOBACCO CONTROL POLICY

Presenter: Heather M. Ross, MPH

Heather M. Ross, MPH

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

In October 2011, the Tobacco Settlement Endowment Trust launched a set of youth advocacy campaigns designed to achieve tobacco control policy outcomes. Three campaigns were developed, each with a different policy focus, including Clean Indoor Air and Tobacco Free Parks Ordinances, 24/7 tobacco free school policies, and Youth Access to Tobacco Ordinances. Students Working Against Tobacco (SWAT) Teams around Oklahoma engaged in a number of strategies to achieve these goals, including community data collection using surveys customized to each campaign's policy goals. This project summarizes the data collected using these surveys to provide insight regarding community member attitudes and support for local tobacco control policy.

A total of 78 SWAT teams collected 3,493 campaign surveys using convenience sampling between October 2011 and January 2013. Descriptive statistics were run to summarize support for local policy amongst adults, youth, tobacco users, non-tobacco users and all respondents. Additional questions assessing observations, attitudes, and beliefs about tobacco were also summarized.

More than 75% of respondents believed all city property should be tobacco free (n=1278), including outdoor places like parks (n=1309). When asked whether they believed local communities should have the right to pass tobacco control ordinances stronger than state law, only 17% of respondents (n=316) answered "no". Nearly 95% (n=1590) said that they would go out more often or just as frequently if restaurants and bars were smokefree. Eighty-four percent (n=1351) said they thought tobacco use should be prohibited on all school property. Tobacco users reported the lowest levels of support for tobacco control policy, though opposition was never more than 50% of respondents.

In terms of the retail environment, youth respondents reported the highest frequency of exposure to tobacco ads in grocery stores, gas stations and drug stores, and the lowest frequency of exposure to warning signs regarding tobacco sales to minors at each location. Additionally, most respondents recognized that youth were more likely to use tobacco if someone they look up to uses tobacco (82%; n=2696).

Though the data collected was not based on a random sample and cannot be generalized to the overall population, the results do provide some insight indicating support for local tobacco control policies, as well as the repeal of preemption at the state level. The data also show that respondents recognize the importance of role-modeling healthy behavior for youth. These findings were true for adults, youth, and in large part tobacco users. Further research using randomized sampling methods should be conducted to validate these findings and support decision making regarding local and statewide tobacco control policy in Oklahoma.

CYSTATHIONINE BETA-SYNTASE OVEREXPRESSION PROMOTES OVARIAN TUMORIGENESIS

Presenter: Sounik Saha

Sounik Saha,¹ Sanjib Bhattacharyya,² Karuna Giri,² Ian R. Lanza,² K. Sreekumar Nair,² Nicholas B. Jennings,³ Cristian Rodriguez-Aguayo,³ Gabriel Lopez-Berestein,³ Eati Basal,² Amy L. Weaver,² Daniel W. Visscher,² William Cliby,² Anil K. Sood,³ Resham Bhattacharya,⁴ Priyabrata Mukherjee¹
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In recent years, hydrogen sulfide (H₂S) attracted a lot of attention for its cytoprotective action and role in angiogenesis. The metabolic enzymes which are responsible for the generation of H₂S *viz.* cystathionine beta-synthase (CBS), cystathionine gamma-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST) have also been observed to be dysregulated in a large number of pathological conditions. Amongst them, the role of CBS however remains poorly understood. Drug resistance and recurrence is a common occurrence in ovarian cancer with an overall 5-year survival of approximately 30%. Our work here finds CBS, a key enzyme required for sulfur amino acid metabolism, to have a critical role in promoting ovarian cancer growth and drug resistance. Overexpression of CBS was observed in a majority of ovarian cancer cell lines utilized in our study compared to normal ovarian surface epithelial cells and also in serous ovarian cancer patient samples from 210 Mayo Clinic cases. Disrupting CBS function in A2780 cells using siRNA or a CBS-specific inhibitor, aminooxyacetic acid reduced proliferation of ovarian cancer cells by dramatically reducing total glutathione levels, H₂S levels and thereby enhancing oxidative stress. Inactivation of anti-apoptotic network and activation of pro-apoptotic cascades also occur upon silencing of CBS. A deeper insight into the intracellular localization of CBS by confocal fluorescence microscopy demonstrated CBS is present in significant amount in the mitochondria and silencing CBS caused mitochondrial superoxide accumulation the output of which is decreased mitochondrial respiration, reduced ATP production and increased ADP-to-ATP ratio. Furthermore, silencing CBS, augmented the cisplatin activity *in vitro* and *in vivo* in an orthotopic model of advanced ovarian cancer. Nanoliposomal delivery of CBS siRNA significantly reduced the number of tumor nodules in a chemoresistant orthotopic mouse model of ovarian cancer. CBS thus presents a viable target for future chemotherapeutic intervention.

MECHANISTIC INSIGHT INTO SUCCESS/FAILURE OF CIRCULATING ANGIOGENIC FACTORS (CAFs) AS PREDICTIVE BIOMARKER FOR ANTI-VEGF THERAPY USING A SYSTEMS PHARMACOLOGY MODELING APPROACH

Presenter: Satish Sharan

Satish Sharan and Sukyung Woo, Department of Pharmaceutical Sciences, School of Pharmacy, University of Oklahoma Health Sciences Center

Purpose: Although antiangiogenic therapies have contributed immensely in the management of cancer, some patients do not respond or gradually develop resistance. Identifying reliable biomarkers for antiangiogenic therapy that can help in identifying which patients are most likely respond to the therapy and show early evidence of resistance is critically important and has been challenging. Circulating angiogenic factors (CAFs), including VEGF, PlGF and sVEGFR, are the most extensively explored biomarkers, but their predictive nature for antiangiogenic therapy has been largely inconsistent. To this regard, we characterized time- and dose-dependent modulation of angiogenic factors in response to VEGFR inhibitor sunitinib (model drug) using a systems pharmacology model, and delineated the contribution of host body and tumor in the total pool of CAF, which has helped in understanding the success/failure of CAFs as predictive biomarker in various studies.

Methods: Temporal kinetic and dynamic profiles of drug concentrations, tumor growth, and CAFs within a therapeutic dose range of sunitinib (20-80 mg/kg) were obtained preclinically and clinically. A mechanism-based, integrative model was developed based on extensive preclinical data and further used to scale up to compare with clinical data through simulations. The model distinguishes differential contribution of host and tumor to the changes in angiogenic markers in response to VEGFR inhibition.

Results: Our model well described time- and dose-dependent changes in CAFs upon sunitinib treatment in a preclinical model system. Daily dosing of sunitinib led to enhanced sustained levels of proangiogenic factors e.g. VEGF, PlGF above the pre-treatment values, which returned to the baseline after treatment withdrawal. Fold change of CAF from baseline correlated well with the therapeutic efficacy of the treatment. Circulation half-life of CAF, 3.5 hr for VEGF and PlGF vs. 22 hr for sVEGFR2, affected their temporal dynamic profiles. The overall tumor contribution to VEGF production was less than 10% of that contributed by host body after sunitinib in preclinical models. Similar phenomenon were observed in clinical studies. Our results suggest that pretreatment VEGF levels that are much higher than those in healthy subjects (approx.80 pg/ml) are more likely to serve as predictive biomarker of antiangiogenic response. The same principal can also hold true for other CAFs.

Conclusion: Our model provides mechanistic insight into the dynamics of angiogenic factors and their origin (tumor vs. host) upon VEGF signaling pathway inhibition. Our simulations also provide a possible explanation for often inconclusive clinical observations on VEGF as a possible predictive biomarker for antiangiogenic therapy.

THE SPINDLE AND KINETOCHORE-ASSOCIATED (Ska) COMPLEX ENHANCES BINDING OF THE ANAPHASE-PROMOTING COMPLEX/CYCLOSOME (APC/C) TO CHROMOSOMES AND PROMOTES MITOTIC EXIT

PRESENTER: Sushama Sivakumar

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The Spindle- and kinetochore-associated (Ska) protein complex is a hetero-trimeric complex required for timely anaphase onset. The major phenotypes seen after siRNA-mediated depletion of Ska are transient alignment defects followed by metaphase arrest that ultimately results in cohesion fatigue. We find that cells depleted of Ska3 arrest at metaphase with only partial degradation of Cyclin B1 and Securin. In cells arrested with microtubule drugs, Ska3-depleted cells exhibit slower mitotic exit when the spindle checkpoint is silenced by inhibition of the checkpoint kinase, Mps1, or when cells are forced to exit mitosis downstream of checkpoint silencing by inactivation of Cdk1. These results suggest that in addition to a role in fostering kinetochore-microtubule attachment and chromosome alignment, the Ska complex has additional functions in promoting anaphase onset. We find that both Ska3 and microtubules promote chromosome association of the Anaphase-Promoting Complex/Cyclosome (APC/C). Chromosome-bound APC/C shows significantly stronger ubiquitylation activity than cytoplasmic APC/C. Forced localization of Ska complex to kinetochores, independent of microtubules, results in enhanced accumulation of APC/C on chromosomes and accelerated Cyclin B1 degradation during induced mitotic exit. We propose that a Ska-microtubule-kinetochore association promotes APC/C localization to chromosomes thereby enhancing anaphase onset and mitotic exit.

SERUM LEVELS OF LBP (LIPOPOLYSACCHARIDE- BINDING PROTEIN) CORRESPOND WITH THE REGRESSION OF TUMOR GROWTH BY THE NITRONE OKN-007 IN F98 RAT GLIOMA MODEL

Presenter: Nataliya Smith

Nataliya Smith, Debra G. Saunders, and Rheal A. Towner

Advanced Magnetic Resonance Center, Oklahoma Medical Research Foundation

Glioblastoma multiforme (GBM), a World Health Organization grade IV glioma, has a poor prognosis in humans despite current treatment options. OKN-007, a disulfonyl derivative of α -phenyl-tert-butyl nitron, has demonstrated anti-glioma effects in several rodent models and is currently in a clinical trial as an investigational drug for recurrent gliomas. The F98 rat glioma model has an infiltrative pattern of growth and has attributes associated with human GBM gliomas. In this study after the MRI detection of F98 gliomas, one group of animals received OKN-007 treatment. It was found the OKN treatment increased survival, decreased tumor growth and decreased tumor volumes.

During the detailed study of assessing the mechanism of OKN-007 action, transcriptional microarray showed that levels of LBP were significantly decreased ($p < 0.05$) between treated and untreated groups of animals. LBP – (liposaccharide-binding protein) which was discovered 27 years ago and named after the ability to bind LPS, is needed to combat infections, and is involved in innate and adaptive immunity. But the main mechanism of action of LBP is still not clear.

The ELISA of LBP performed on tissue lysates from animals showed expression differences during the therapy. The levels of LBP in the tumor bearing animals were significantly elevated compared to the non-tumor control group, and that the OKN-007 treatment brought the levels of LBP close to the non-tumor controls. Moreover, we also performed the ELISA of LBP using the blood serum from the same animals. The analysis of LBP in blood serum confirmed that the LBP can serve as a serum biomarker that can predict the therapy outcome of OKN-007 in gliomas. The identification of this new serum biomarker could help in the future diagnosis and assessment of treatment response for GBM patients.

DISCUSSING TOBACCO PREVENTION AND SECONDHAND SMOKE EXPOSURE WITH PATIENTS AND PARENTS: ASSESSING THE TRAINING AND CONFIDENCE OF INCOMING PEDIATRIC AND FAMILY MEDICINE INTERNS

Presenter: Kristina I. Suorsa

Kristina I. Suorsa^{1,2}; Leslie M. Driskill, M.S.^{2,3}; Tina M. Belt, M.D.³; Larissa N. Hines, M.D.³; Julia M. Stoltenberg, M.D.³; Monique Naifeh, M.D.³; Theodore L. Wagener, Ph.D.^{2,3}; Stephen R. Gillaspay, Ph.D.^{2,3}

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BACKGROUND: Limited information is available assessing physician training and confidence related to discussing smoking cessation and second hand smoke exposure 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.

METHOD: Incoming medical interns completed questions about previous training in tobacco prevention/secondhand smoke exposure and levels of confidence in their ability to provide education and assistance about smoking cessation. Confidence in addressing smoking cessation was assessed using a 6-item, Likert scale, with item scores ranging from 1 (Not confident at all) to 7 (Very confident).

RESULTS: Twenty-five (82.6%) participants completed this study. Sixty percent were PIs and 40% were FMIs. Participants had a mean age of 26.7 years (SD=1.83) and 68% were female. Twelve (80%) PIs reported previous training/education in tobacco prevention and control or second hand smoking during undergraduate or medical school, compared to 5 (50%) FMIs. Also, mean confidence scores for addressing smoking cessation in patients >12 years and parents were 5.71 (SD=.75) and 5.59 (SD=.87), respectively. These findings indicated that although new interns were "moderately confident" discussing this topic with patients and families, there was still some room for improvement. For individual items, PIs were slightly less comfortable prescribing nicotine replacement medications to both children (M=4.87) and parents (M=4.73) than FMIs (child M=6.00 and parent M=5.40). Other item scores related to providing guidance, advice, assessment, recommendations, and referral to a quit line for smoking cessation were generally consistent between both groups, ranging from 5.2 to 6.2 for PIs and 5.10 to 6.30 for FMIs.

CONCLUSION: This study identified the importance of training in tobacco use prevention and secondhand smoke exposure during residency. Also, interns could benefit from additional experiences addressing smoking cessation in order to improve their level of confidence with these important topics, specifically in prescribing nicotine replacement medications.

PROMOTING REGULAR SCREENING MAMMOGRAPHY IN AN AMERICAN INDIAN COMMUNITY IN OKLAHOMA

Presenter: Eleni Tolma, PhD

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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 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 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). Intervention pilot testing is in process (Aim 3). Full intervention dissemination and evaluation (Aim 4) will begin soon.

Conclusion: It is feasible to partner with AI/AN community and clinical members to develop a culturally sensitive, community-driven, and theoretically-framed breast cancer screening intervention. It is hopeful that this approach will lead to pronounced improvement in screening mammography uptake and ultimately to improved clinical outcomes.

ELTD1 AS A TARGET FOR ANTI-CANCER THERAPY IN RODENT GLIOMAS

Presenter: Rheal A. Towner

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Despite current therapies, glioblastoma multiforme (GBM) is a devastating cancer with a very poor prognosis. Specific protein biomarkers for GBM enable not only new prognostic avenues to tailor treatment, but valuable therapeutic targets to interfere with GBM growth. We recently discovered a new biomarker for high-grade gliomas, ELTD1 (epidermal growth factor, latrophilin, and 7 transmembrane domain-containing protein 1 on chromosome 1), via a novel bioinformatics approach, GAMMA (Global microarray meta-analysis). ELTD1 was found to be significantly higher ($p < 0.05$) in high-grade gliomas (50 patients) compared with low-grade gliomas (21 patients). ELTD1 gene expression was found to be associated with tumor grade, survival across grade, and an increase in the mesenchymal subtype. From our previous results we hypothesized that ELTD1 may be a potential therapeutic target in high-grade gliomas. We tested the hypothesis in an orthotopic GL261 mouse glioma model in animals treated with an anti-ELTD1 antibody, compared to those that were treated with an anti-VEGF antibody or an anti-c-Met antibody, and untreated tumors. Tumor volumes were measured by morphological magnetic resonance imaging (MRI). Our data in orthotopic GL261 glioma-bearing mice shows that injection of anti-ELTD1 antibodies lead to a significant decrease in tumor volumes ($p < 0.0001$) and a significant increase in animal survival ($p < 0.05$), superior to that achieved by a mouse anti-VEGF antibody or an antibody against c-Met, when compared to untreated mice. Tumor volumes were obtained at various time-points, and compared at 21 days following intracerebral implantation of GL261 cells in male C57BL6 mice. These tumor volumes at 21 days were 86.03 ± 41.54 mm³ for untreated mice ($n=5$); 13.04 ± 5.35 mm³ for anti-ELTD1 treated mice ($n=5$); 33.16 ± 12.48 mm³ for anti-VEGF treated mice ($n=4$); and 28.49 ± 11.11 mm³ for anti-c-Met treated mice ($n=5$). The mean days of survival for untreated, ELTD1, VEGF or c-Met treatment groups were 23.8 ± 1.79 , 28.2 ± 2.39 , 27 ± 1.15 or 27 ± 1.87 days, respectively. These pre-clinical results indicate that an additional therapy in the form of an anti-ELTD1 antibody either as a sole agent or in combination with current or new therapies could potentially provide high-grade glioma patients with a better prognostic outcome.

PHARMACOKINETICS OF DT-310, A NOVEL ANTICANCER COMPOUND, IN MICE

Presenter: Rahul Kumar Verma

Rahul Kumar Verma, Lora C. Bailey-Downs, Alexa Kunch, Bryan C. Disch, Anja Bastian, Robert E. Hurst, Michael A. Ihnat and Lucila Garcia-Contreras
College of Pharmacy, University of Oklahoma Health Science Center

Purpose- DT-310 is a novel compound with encouraging anticancer activity against breast, bladder, pancreatic and colon cancer cells. In order best route of administration, dose and dose regimen, the disposition of DT-310 after intravenous injection was evaluated in mice.

Method- Balb/c mice were employed in this study and gender difference was addressed by using male and female mice. The dosing solution (6.5 mg/kg) of DT310 was injected as bolus through the retro-orbital vein. Blood was collected by cardiac puncture (as a terminal procedure) at the time schedule of 0 (pre-dose), 5, 10, 15, 30 minutes, 2h, 8h, and 24h after dosing. Three animals were used per time point and their plasma was pooled into a single sample for extraction and HPLC analysis of DT310. Pharmacokinetic parameters, including The area under the curve ($AUC_{0-\infty}$), elimination half-life ($t_{1/2}$), steady state volume distribution (V_{ss}), clearance (CL) and mean residence time (MRT) were determined using non-compartmental model using WinNonlin software.

Results- In both mice genders, DT-310 had a biphasic profile: The first phase (distribution/elimination) was fast (< 15 minutes), followed by a slower second phase (elimination, approximately 7 hours). The $AUC_{0-\infty}$, $t_{1/2}$, V_{ss} , CL and MRT were 5.924 $\mu\text{g} \times \text{h/ml}$, 0.096 h, 289.45 ml/kg, 1091.932 ml/h/kg and 0.256 h in male and 6.092 $\mu\text{g} \times \text{h/ml}$, 0.11 h, 295.241 ml/kg, 1062.739 ml/h/kg and 0.270 h in female mice respectively. DT-310 showed first order pharmacokinetics with short $t_{1/2}$ and appreciably greater CL and V_z . Except for a slightly longer half-life ($t_{1/2}$) observed in female mice after IV administration of DT-310, there were no differences in the remaining PK parameters characterizing the disposition of DT-310 between male and female mice.

Conclusion- Based on the PK parameters DT-310 would have a longer effect if administered by non-parenteral route and larger doses should be considered for a therapeutic efficacy.

THE MECHANISMS OF ZINC PROTOPORPHYRIN-INDUCED SUPPRESSION OF β -CATENIN EXPRESSION IN HUMAN CANCER CELLS

Presenter: Shuai Wang

Shuai Wang, Bethany N. Hannafon, and Wei-Qun Ding

Department of Pathology, University of Oklahoma Health Sciences Center

Zinc protoporphyrin (ZnPP), an established heme oxygenase-1 (HO-1) inhibitor, has been reported to have anticancer activity in *in vitro* and *in vivo* model systems. However, the mechanisms of ZnPP's anticancer action remain elusive and seem to be HO-1 independent. We have recently demonstrated that ZnPP rapidly and dramatically suppresses the expression of β -catenin, a key player in the canonical Wnt signaling pathway, in human cancer cells. The present study is aimed at characterizing the cellular and molecular mechanisms of ZnPP-induced suppression of β -catenin expression in cancer cells. We found that pretreatment of A2780 (human ovarian cancer) and DU145 (human prostate cancer) cells with Brefeldin A and Monensin, two inhibitors of cellular protein transportation, significantly recovered β -catenin protein level in ZnPP treated cells in a concentration- and time-dependent manner. Furthermore, extracellular β -catenin protein was barely detectable in the media culturing ZnPP-treated cells, and the spectrums of secreted proteins were similar in untreated and ZnPP-treated cells. These results suggest that ZnPP induces intracellular transportation of β -catenin thereby leading to its protein degradation in cancer cells. To our surprise, however, ZnPP globally and significantly inhibited cellular proteasome activity as assayed with a fluorogenic substrate (Suc-LLVY-AMC) and induced accumulation of poly-ubiquitinated proteins in A2780 cells. Based on these observations we conclude that ZnPP-induced β -catenin degradation is likely a cellular compartment specific event, and intracellular transportation of β -catenin protein is critical for ZnPP-induced degradation. A GFP- β -catenin expression construct has been established to study how intracellular β -catenin is transported and at what cellular compartment β -catenin is degraded after ZnPP treatment in our model systems. This investigation will reveal novel cellular mechanisms of ZnPP's anticancer action and firmly establish ZnPP as a potent inhibitor of the canonical Wnt signaling pathway.

TOBACCO CONTROL AND POLICY IN OKLAHOMA

Presenter: Ashley H. White, MPH

Ashley H. White and Lisa H. Yadon

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

Oklahoma is one of only 10 states that have preemptive state tobacco control legislation which prohibits localities from enacting tobacco control laws more stringent than the state. This legislation, the Oklahoma Smoking in Public Places Act, was enacted in 1987 and, is often referred to simply as “preemption”. In 1996 Oklahoma became the 14th state to file suit against the tobacco industry to recover tax dollars lost due to tobacco related morbidity and mortality. In 1998 the Master Settlement Agreement (MSA) was reached with the tobacco industry. As a result, the tobacco industry was ordered to pay Oklahoma approximately \$2 billion over the first 25 years of the settlement. The Oklahoma Tobacco Settlement Endowment Trust (TSET) was formed in 2000 through a voter-approved constitutional amendment. Oklahoma is the only state to have constitutionally protected the majority of their MSA funds in an endowment. Only the interest and dividend earnings are spent and only on programs aimed to improve the health of Oklahomans. In 2004 TSET launched the Communities of Excellence in Tobacco Control (CX) program. Through this program, community coalitions are funded by grants to implement comprehensive tobacco control programs. One of the actions proven most effective to decrease tobacco use is the passage of community based tobacco control policies. CX grantees in Oklahoma are limited in their activities because of the preemptive state legislation. However, through guidance from TSET and the Oklahoma State Department of Health, grantees have excelled in working with schools, businesses and cities/townships to promote policies and programs aimed to reduce tobacco use at the local level. Through June 2013, CX grantees have contributed to the passage of 274 tobacco free school policies, 223 tobacco free worksite policies, 287 clean indoor air ordinances/policies covering city-owned property and 48 recreational area policies which cover 522 facilities.

Despite the restrictive preemptive legislation, the Oklahoma CX programs have found innovative ways to affect policy and social norms change within communities. Through the passage of over 750 local policies and ordinances, the CX programs have helped to decrease cigarette consumption in Oklahoma from 103 packs per capita in 2003 to 71 packs per capita in 2012. This reduction in cigarette consumption should have a significant impact on morbidity and mortality from smoking related illness and disease.

STATE-LEVEL CORRELATES OF UNASSISTED SMOKING QUIT ATTEMPTS AND SUCCESS

Presenter: Mary B. Williams, PhD

Mary B. Williams, PhD; Laura A. Beebe, PhD; and Barbara R. Neas, PhD

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

Background: Although the majority of former smokers report quitting without assistance and the majority of smokers attempting to quit do so without assistance, research in the area of unassisted cessation is limited. Some have argued that population-based interventions, such as tobacco control programs, policies, and social norms may contribute to unassisted quit attempts and successful cessation.

Methods: The current study used the 2003 special Cessation Supplement of the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) to estimate weighted state unassisted quit attempt and success rates, and assessed whether these rates varied. Linear regression analyses were used to examine whether state-level unassisted quit attempt and success rates were related to state-level policies and social norms. State policy factors investigated were tobacco control program funding, tobacco taxes, and smoke-free air policies, while tobacco social norm indicators included change in smoking prevalence and state anti-smoking sentiment.

Results: Consistent with other studies, the current study found the majority of smokers attempted to quit without assistance. This study also found unassisted quit attempt rates were higher than assisted attempt rates in every state and DC. Furthermore, unassisted quit success rates were higher than assisted quit success rates in most states; however, some states had higher assisted quit success rates. State-level factors associated with unassisted quit attempt rates included anti-smoking sentiment and tobacco taxes; however, no significant relationships were uncovered between unassisted quit success rates and state-level factors.

Conclusions: These results suggest that state-level factors may be more important in motivating smokers to attempt to quit, and other unmeasured state or individual factors may be related to quit success. These findings are of considerable public health significance as they can guide states and tobacco control programs to plan effective policies and programs to prompt more smokers to attempt quitting both with and without assistance.

GOLD NANOPARTICLES INHIBIT TUMOR GROWTH AND METASTASIS BY REVERSING EMT AND DECREASING STEM-LIKE CELLS POPULATION

Presenter: Xunhao Xiong

Xunhao Xiong¹, Rochelle R. Arvizo², Sounik Saha¹, Enfeng Wang², Resham Bhattacharya¹, Priyabrata Mukherjee¹

¹Peggy and Charles Stephenson Oklahoma Cancer Center, University of Oklahoma Health Sciences Center, OKC, OK 73104; ²Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, MN 55905

Gold nanoparticles (AuNPs), have attracted wide attention in various biomedical applications because they are biocompatible, easy to synthesize, characterize, and surface modify. Although major efforts in biomedical nanotechnology have concentrated on drug delivery and biosensing applications, biological characterization of unmodified nanoparticles remains under-investigated. Herein we demonstrate that unmodified AuNPs inhibit the proliferation of cancer cells in a size- and concentration-dependent manner by abrogating MAPK-signaling. In addition, AuNP treatment alters the expression profile of a number of cytokines. These AuNPs reverse epithelial-mesenchymal transition (EMT) in cancer cells by reducing secretion of some of these proteins involved in EMT, up-regulating E-Cadherin, and down-regulating Snail, N-Cadherin, and Vimentin. Most interestingly, AuNPs inhibit the expression of cancer stem cells markers such as ALDH1, CD24, CD44 and CD133 in ovarian cancer cells. Simultaneously, the side population of these cancer cells was decreased after AuNP treatment. We also set up two separate orthotopic models of ovarian cancer and demonstrated that inhibition of MAPK signaling and reversal of EMT upon AuNP treatment inhibits tumor growth and metastasis. The ability of a single self-therapeutic nanoparticle to abrogate signaling cascades of multiple growth factors and to inhibit cancer stem cells population is distinctive and purports possible medical application. Our findings present a unique biological function of unmodified nanoparticles and pave the way for future investigation on the use of inorganic nanoparticles as a class of antitumor and anti-metastatic agents.

Shared Resources

Biospecimen Acquisition Core and Bank

About the Core

The Stephenson Biospecimen Acquisition Core and Bank was established in 2006 to provide specimen collection, storage and processing services to cancer center members and other investigators. The Core's Biospecimen Bank currently contains over 30,000 aliquotted samples, including tissue, blood, plasma, serum, cell and buccal samples. The Core utilizes an IRB-approved Universal Consent that allows patients at the Stephenson Cancer Center, OU Physicians or OU Medical Center to donate tissue or blood to the Biospecimen Bank. Over 3,500 patients have consented to participate. The Core has large specimen collections of gynecologic cancers and pancreatic cancer to support research in those disease sites.

The Core also provides specimen collection, processing and shipping services to the large and active clinical research program at the Stephenson Cancer Center. Since 2008 the Core has supported over 300 clinical trials, including large tissue trials such as GOG 136, GOG 210, GOG 221 and NCI's SUCCEED trial. The Stephenson Cancer Center was the lead tissue accrual site in each.

The Core's main facility is in the Stanton L. Young Biomedical Research Center (BRC) on the OUHSC campus. A satellite facility in the Stephenson Cancer Center building is dedicated to supporting the Oklahoma TSET Phase I program with specimen processing and shipping services.

Services Offered

- 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 specimens are not available in the Biospecimen Bank, Core staff can help facilitate the procurement of specimens from the appropriate sources. The Core also supports protocol-driven specimen collection for specific research projects.

Core Information Systems

In conjunction with the Clinical Trials Office, the Biospecimen Acquisition Core and Bank uses a HIPAA and 21 CFR Part 11 compliant clinical trials management system (Velos eResearch). An integrated specimen inventory system (Velos eSample) is used to catalog banked specimens. Data are stored on a secure server with access limited to key protocol personnel.

Contact Information

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

Biostatistics Core

Overview

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. Core services include:

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: Basic 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 additional information, please email the Biostatistics Core at SCC-Biostat@ouhsc.edu.

Cancer Tissue Pathology Core

About the Core

The goal of the Cancer Tissue Pathology Core is to provide 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.

Core equipment includes a Leica Motorized Rotary Microtome, a Leica CM1950 Cryostat, a Leica BOND-III automated IHC / ISH-stainer, and a Veridiam Automated Tissue Arrayer along with upright and inverted microscopes, and bright field and fluorescence microscopy. Aperio whole slide scanning services are available through the Department of Pathology.

Services Offered

- Histology and Immunohistochemistry
- Tissue Microarray (TMA)
- Digitized Slides and Image Analysis
- Photographic and Imaging Services
- Molecular Biology Services

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 and Operating Procedures

- Agilent SureScan Microarray Scanner System
- Biorad CFX96™ Touch Real-Time PCR Detection System
- Perkin Elmer EnVision® Multilabel Reader
- Biorad Experion™ Automated Electrophoresis Station
- Agilent 2100 Bioanalyzer
- Arrayit Nanoprint™
- XFe 96 Extracellular Flux Analyzer
- Biorad QX100 Droplet Digital PCR
- Perkin Elmer Operetta
- Janus Automated Workstation
- Arrayit Spotware Scanner

Contact

For more information about the Core please contact:

Muralidharan Jayaraman, PhD

Director of Research Core Operations

Email: muralidharan-jayaraman@ouhsc.edu

Phone: 405-271-6890

Clinical Trials Office

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

- 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. More information can be found below:

Contact Information

Administrative Office: 405-271-8777

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

Molecular Imaging Core

About the Core

The Molecular Imaging Core provides non-invasive optical imaging services to Stephenson members and other investigators at the OU Health Sciences Center and neighboring institutions. The Core includes the following equipment (click on links below for description and images):

- 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
- Leica Fluorescence Stereo Microscope
- INVIVO 400 and 500 Hypoxia Workstations

Services Offered

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

Contact Information

For more information please contact:

Rajagopal Ramesh, PhD

Director, Molecular Imaging Core

rajagopal-ramesh@ouhsc.edu

Proposal Services

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 Core by calling

Phone: 405-271-1878

Email: SCC-PM@ouhsc.edu,

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

Special Populations Core

About the Core

The Special Populations Core (SPC) at the Stephenson Cancer Center provides investigators with consultation and collaboration services, grant development, manuscript preparation, and other research assistance for projects that have a focus on minority populations. The SPC has a special focus on assisting researchers who desire to work with American Indian populations.

Services Offered

- Identification of appropriate partners, preferably as early as possible in the research planning process;
- Identification of appropriate Stephenson investigators in response to tribal requests for research partners to pursue tribally-initiated research questions;
- Facilitation of meetings between STEPHENSON investigators and potential minority partners;
- Consultation about appropriate structuring of tribal-university memorandums of understanding to detail collaboration arrangements (with emphases on short- and long-term responsibilities of investigators with respect to tribal governments, organizations, and communities);
- Facilitation in processing tribal subcontracts and letters / resolutions of support;
- Consultation in preparing IRB applications for tribal and / or Indian Health Service;
- Ongoing assistance in managing community-university relationships as the study is being conducted;
- Consultation about concluding studies and reporting findings back to tribes, tribal organizations, tribal and / or Indian Health Service IRB and participants (as appropriate);
- Serve as the primary point of contact between the Stephenson and Oklahoma tribes, tribal health systems, the Oklahoma City Indian Health Service and the Oklahoma City Area Inter-Tribal Health Board / Southern Plains Epidemiology Center.

Contact Information

For more information about Core services please contact:

Lancer Stephens, PhD

Director, Special Populations Core

Phone: 405-271-8001, ext. 46758

lancer-stephens@ouhsc.edu

OMRF Nuclear Magnetic Resonance Core

About the Core

Construction of the shared instrument facility and installation of the MRI magnet and hardware was completed in Sept. 2004. It is shared by researchers at the Oklahoma Medical Research Foundation (OMRF) and the University of Oklahoma Health Sciences Center (OUHSC) primarily as well as other researchers in Oklahoma. Our biomedical research interests include, but are not limited to, cancer biology, neurological disorders and cardiovascular pathologies. These themes are addressed with techniques such as basic morphological MRI (e.g. T1, T2 imaging), dynamic contrast-enhanced MRI (DCE) to establish location and extent of pathological lesions, MR angiography (MRA) to visualize vascularization, functional MRI (fMRI) to monitor tissue/organ response given a challenge function, and MR spectroscopy (MRS) to follow metabolic changes during a disease processes.

A particular strength of the facility is recent developments in the use of molecular targeting agents, which couple a MRI contrast agent (such as gadolinium complexes or ferromagnetic particles) with antibodies specific for cellular receptors or other antigens. This form of contrast enhanced imaging, allows in vivo visualization of molecular events. Many of the studies utilize transgenic murine models. The use of transgenic mice has dramatically advanced our ability to analyze and understand the molecular basis of various diseases. However, we are not limited to mice. Subjects up to approximately 20 cm in axial diameter may be imaged.

The Oklahoma INBRE, OMRF COBRE, and OCAST (Oklahoma Center for the Advancement of Science and Technology) funding provides the facility with infrastructure funds for investigators to obtain in vivo non-invasive functional, morphological and molecular information on various disease models focusing on neurological diseases and cancer detection and therapeutic agent assessments, and cardiovascular disease.

In 2008, OMRF added a second, more powerful MRI to the facility. This 11.7 Tesla magnet uses super-cooled liquid helium that circulates continuously through its coils to generate a magnetic field that is 200,000 times stronger than the Earth's.

Although the MRI is commonplace in human medicine, there are no more than a handful of small-animal MRI facilities in the country with magnets as strong as OMRF's.

Contact Information

MRI FACILITY

OMRF, Mail Stop 60

825 NE 13th Street

Oklahoma City, OK 73104

Phone: (405) 271-7232

Fax: (405) 271-7254

Email: debra-saunders@omrf.org

OMRF Next Generation DNA Sequencing Core

About the Core

The OMRF Next Generation Sequencing (NGS) facility is a universally accessible resource able to provide investigators with massive amounts of DNA sequence in a relatively short period of time. Our Hiseq 2000 is able to generate 3.2 billion reads for a total of 640 Gigabases in a single 10-day run while our Miseq is able to generate 5 million reads for a total of 1.5 Gigabases in a single 24 hour run.

The facility is capable of processing and analyzing all forms of sequencing projects, including whole genome sequencing, custom targeted resequencing including exome capture, RNA-seq, ChIP-seq, and MethylCap-Seq. Study sample sizes can range from singletons to hundreds or even a thousand samples.

Contact Information

For more information contact:

Dr. Graham Wiley

OMRF, Room T2101

wileyg@omrf.org

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.

Core services include:

- 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: microgen_support@ouhsc.edu

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

Mass Spectrometry and Proteomics information: lmblr_help@ouhsc.edu

For additional inquiries:

Dr. Allison Gillaspy, Director
405-271-2337 (ext. 1)
allison-gillaspy@ouhsc.edu

Cancer Center Research Programs

Basic 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 Basic 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

Janknecht, Ralf, PhD

Program Members

Ali, Naushad, PhD

Battiste, James, MD, PhD

Chen, Hong, PhD

Chung, Jun, PhD

Crawford, David F. MD, PhD

Csisar, Anna, PhD

Dhanasekaran, Danny, PhD

Frazer, J. Kimble, MD

Gorbsky, Gary, PhD

Griffin, Courtney, PhD

Hanas, Jay, PhD

Hanigan, Marie, PhD

Howard, Eric, PhD

Hurst, Robert, PhD

Huycke, Mark, MD

Jones, David, PhD

Kaul, Rashmi, PhD

Kreth, Jens, PhD

Li, Guangpu, PhD

Li, Shibo, MD

Lin, HK, PhD

Lin, Jialing, PhD

Matsumoto, Hiryuki, PhD

Merritt, Justin, PhD

Mooers, Blaine, PhD

Olson, Lorin, PhD

Pezza, Roberto, PhD

Pioszak, Augen, PhD

Qi, Felicia, PhD

Queimado, Lurders, MD, PhD

Rankin, Susannah, PhD

Song, Ping, PhD

Song, Young Hwa, PhD

Sonntag, William, PhD

Sun, Xiao-Hong, PhD

Teague, Kent, PhD

Towner, Rheal, PhD

West, Christopher, PhD

Zenewicz, Lauren, PhD

Zhang, Xin, MD, PhD

Zhao, Zhizhuang (Joe), PhD

Gynecologic Cancers 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

McMeekin, Scott, MD

Program Members

Aldoohan, Sulaiman, PhD

Benbrook, Doris, PhD

Bhattacharya, Resham, PhD

Ding, Wei-Qun, PhD

Dooley, William, MD

Ha, Ji Hee, PhD

Hilderbrand, William, PhD

Husain, Sanam, MD

Landrum, Lisa, MD, PhD

Mannel, Robert, MD

Matts, Robert, PhD

Matzo, Marianne, PhD, RN

Moore, Kathleen, MD

Moxley, Katherine, MD

Mukherjee, Priyabrata, PhD

Rundle, Dana, PhD

Spicer, Leon, PhD

Walker, Joan, MD

Wu, Dee, PhD

Zuna, Rosemary, 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, micro 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

Ramesh, Rajogopal, PhD

Program Members

Algan, Ozer, MD

Aravindan, Natarajan, PhD

Awasthi, Shanjana, PhD

Awasthi, Vibhudutta, PhD

Berlin, Kenneth, PhD

Chen, Wei, PhD

Cherry, Mohamad, MD

Fung, Kar-Ming, MD, PhD

Gali, Hariprasad, PhD

Garcia-Contreras, Lucila, PhD

Harrison, Roger, PhD

Mohammed, Altaf, PhD

Munshi, Anupama, PhD

Pant, Shubham, MD

Patlolla, Jagan, PhD

Piao, Daqing, PhD

Rahaim, Ronald, PhD

Rao, CV, PhD

Schmidtke, David, PhD

Selby, George, MD

Sikavitsas, Vassilios, PhD

Slaton, Joel, MD

Hays, Franklin, PhD
Herman, Terence, MD
Holter-Chakrabarty, Jennifer, MD
Houchen, Courtney, MD
Hubin, Timothy, PhD
Ihnat, Michael, PhD
Janakiram, Naveena, PhD
Kurkjian, Carla, MD
Lang, Mark, PhD
Liu, Hong, PhD
Ma, Jian-xing, MD, PhD
Mao, Chuanbin, PhD
Matthieson, Chance, MD
McNall-Knapp, Rene, MD

Sureban, Sripathi, PhD
Tanaka, Takemi, PhD
Tweten, Rodney, PhD
Vega, Kenneth, MD
Woo, Sukyung, PhD
Wren, Jonathan, PhD
Yamada, Hiroshi, PhD
You, Youngiae, PhD
Yue, Wei, PhD
Zhao, Daniel, PhD
Zheng, Bin, PhD
Zou, Ming-Hui, MD, 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

Doescher, Mark, MD, MSPH

Program Members

Bacharach, Marianne, MD
Basara, Heather, PhD
Beebe, Laura, PhD
Blanchard, Jessica, PhD
Brand, Michael, PhD
Branscum, Paul, PhD
Campbell, Janis, PhD
Cheney, Marshall, PhD
Ciro, Carrie, PhD
Craft, Melissa, PhD, RN
Darling, Tom, PhD
Deal, Randolph, PhD
Ding, Kai, PhD
Dwyer, Kathleen, PhD, RN
Eschiti, Valerie, PhD, RN
Espinosa-Varas, Blas, PhD
Foster, Morris, PhD
Friedman, Jack, PhD
Ge, Xun, PhD

Jernigan, Valarie, DrPH
Jervis, Lori, PhD
Khan, Ahsan, MD
Knehans, Allen, W., PhD
Laux, Fritz, PhD
Mold, James, MD
Nagykaldi, Zsolt, PhD
Phillips, Margaret, PhD
Rogers, Carol, PhD
Rhoades, Dorothy, MD, MPH
Shay, Christina, PhD
Showers, Carolin, PhD
Sisson, Susan, PhD, CHES
Skrepnek, Grant, PhD
Smith, Patsy, PhD
Spicer, Paul, PhD
Stoner, Julie, PhD
Tolma, Eleni, PhD
Vesely, Sara, PhD

Hallford, Gene, PhD
Hamm, Robert, PhD
Holtzclaw, Barbara, J., PhD
Hsieh, Elaine, PhD

Wagener, Ted, PhD
Wong, Norman, PhD
Yeh, Fawn, PhD

Cancer Center Researchers & Research Interests

Naushad Ali, PhD

Statement of the Principal Investigator's research interests:

My research interests have been on positive strand RNA virus-induced diseases, translational regulation in normal and disease conditions, cancer stem cells and hepatocarcinogenesis. My current research goals are:

- to understand molecular mechanism (s) of virus-induced initiation of hepatocellular carcinoma (HCC)
- to identify and characterize cancer stem cells generated during chronic hepatitis C virus (HCV) infection and initiation of liver cancer
- to investigate cell signaling pathways that promote transition from pre-neoplastic (cirrhosis) to malignant conditions.

-

Our recent studies have revealed a positive correlation between HCV replication and expression of tumor/cancer stem cell (CSC) marker, doublecortin-like kinase 1 (DCLK1). Although normal human liver tissues and isolated hepatocytes lack DCLK1 expression, the spheroids derived from normal human hepatocytes, HCV-infected liver and hepatoma cell-derived tumor xenografts exhibit extensive DCLK1 expression. We have further shown that downregulation of DCLK1 levels by specific siRNAs inhibits HCV replication in cell culture and tumor growth in mouse xenograft models.

We are currently investigating the impacts of DCLK1 overexpression on cellular functions, and signaling pathways that promote hepatocarcinogenesis. We use HCV replicon and infection models, transcriptome analysis, hepatic spheroid/organoid culture, liver tissues derived from HCC and HCV patients, and mouse models to investigate hypothesis-driven projects on liver cancer. Our preliminary finding that DCLK1 overexpression may initiate HCC through activation of inflammatory and MAPK signaling pathways is being tested in various models.

It is my belief that extensive investigations on DCLK1 gene regulation and delineation of its tumorigenic potential will provide insight into the molecular mechanisms of HCV-induced hepatocarcinogenesis, and will further aid in the development of novel anti-HCV and anti-tumor treatments by targeting DCLK1.

Sulaiman D. Aldoohan, PhD, DABR

Assistant Professor

Co- Director of Medical Physics Residency Program

The University of Oklahoma, Health Sciences Center

Radiological Sciences Department, Oklahoma, OK 73104

Publications:

1. A. Maghsoodpour, **S. Aldoohan** "An Experimental Study of the Effects of Different Beam-Hardening Filters on $CTDI_{vol}$ and Low-Contrast Image Detectability in a CT Scanner," American Association of Physicists in Medicine (AAPM) 2013 annual meeting, Indianapolis, IN
2. **S. D. Aldoohan** "A proposed Study For Evaluating Quality Assessment Procedures For A Computed Radiography System", American Association of Physicists in Medicine (AAPM) annual meeting, Milwaukee, WI, Book of Abstracts, (1997) (A).
3. J. A. Urbon and **S. D. Aldoohan** "Simulated Human Tissue Equivalent Muscle, Fat and Bone Quality Control Phantom Constructed From a Novel Polysaccharide Material TX-150", American Association of Physicists in Medicine (AAPM), annual meeting, Philadelphia, Pennsylvania, Book of Abstracts, (1996) (A).
4. M. W. Groch; J. A. Urbon; W. D. Erwin; **S. D. Aldoohan** " An MRI Tissue Equivalent Lesion Phantom Using A Novel Polysaccharide Material" Magnetic Resonance Imaging, Vol. 9, pp. 417 – 421, (1991).

Research Support (Last Five Years)

- 1- CT Protocols Optimization for Pediatric Patients having Cerebrospinal Fluid Shunt (work in progress)
- 2- Computing Detective Quantum Efficiency (DQE) in Multislice CT scanner (work in progress)
- 3- Dose Reduction in Multislice CT scanning protocols using different beam hardening filters (work in progress)
- 4- Evaluating factors affecting image quality in Digital Breast Tomosynthesis (DBT) imaging

Natarajan Aravindan, PhD

Department of Radiation Oncology
University of Oklahoma Health Sciences Center

TITLE AND AFFILIATION

Assistant Professor of Radiation Biology, Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Department of Anesthesiology, OUHSC

Department of Pathology, OUHSC

Associate Member, Experimental Therapeutics/Cancer Biology, Stephenson Oklahoma Cancer Institute, Oklahoma City, OK,

Faculty (Level 4) Graduate College, OUHSC

Faculty Member Reynolds Oklahoma Center on Aging, Oklahoma City, OK

Oklahoma Tobacco Research Center (OTRC), Oklahoma City, OK

Oklahoma Center for Neuroscience (OCNS), Oklahoma City, OK

PEER REVIEWED PUBLICATIONS

Research Articles: 54

Books and Monographs: 3

Abstracts: 105

RESEARCH INTERESTS

The major commitment of my research has been dedicated towards better understanding of the radiobiological events that happen both in tumor and in normal cellular systems and providing protection or sensitization. To that end, my laboratory research has been related to potentiate radiotherapy for the better benefit of cancer patients and also to identify latent deliverables as radio-protectants to improve the quality of life. Primary research areas include, (i) Free radical biology, cancer models, cell signaling (ii) Radiation health effects, bystander signaling, (iii) Transcriptional Machinery, (iv) Tumor relapse, recurrence, invasion and metastasis, (v) radiobiology, (vi) Developmental therapeutics, (vii) Tumor Targeted delivery, (viii) Ployphenols as anti-cancer deliverables, (ix) Cancer Chemoprevention, etc.

Hope Baluh, MD

Hope Baluh is the principal investigator. Interests include Native American Health. Preventative care in the Indian Health Care system including screening and establishment of a comprehensive accurate tumor registry, electronic records that facilitate screening and follow up, outreach to rural Native American populations, and streamlining processes to assist in preventative care.

Additional interests include development of algorithms within the Indian Health System to optimize surgical care of those patients affected by cancer and bariatric surgery in rural Oklahoma.

James D. Battiste, MD, PhD

Assistant Professor in the Department of Neurology at OU Health Sciences Center

Major area of interest:

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 growth 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 A. Beebe, PhD

Laura A. Beebe, PhD is the Principal Investigator for the Oklahoma site of the ANBL research study. As the Co-Director for Research and Evaluation within the Oklahoma Tobacco Research Center (OTRC) and through her role as a faculty member within the College of Public Health, Dr. Beebe has more than 16 years of experience conducting research and evaluation in tobacco control and prevention, with a focus on tobacco cessation and community-based strategies in American Indian communities.

Resham Bhattacharya, PhD

FOCUS AREA: MAJOR INTEREST OF BHATTACHARYA LAB

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.

Jessica Blanchard, PhD

Dr. Jessica Blanchard is a faculty member in the Department of Anthropology at the University of Oklahoma.

Hong Chen, PhD

Principal Investigator's Research Interests:

Dr. Hong Chen's research program has centered on unveiling the endocytic regulation of vascular development and remodeling. 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 requirement of epsins in the developing and adult vascular system. 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 vascular system, are poorly understood. We recently characterized an important regulatory role of epsins in vascular remodeling and have preliminary projects implicating the importance of epsins in inflammation and cancer progression.

Wei R. Chen, PhD

Director, Center for Interdisciplinary Biomedical Education and Research (CIBER)
Assistant Dean, College of Mathematics and Science
Professor, Department of Engineering and Physics
University of Central Oklahoma

LASER IMMUNOTHERAPY FOR TREATMENT OF METASTATIC CANCERS

Combining laser-photothermal interaction and a novel immunoadjuvant, we have developed a novel cancer treatment modality for metastatic cancers – Laser Immunotherapy. Our pre-clinical experiments and preliminary clinical trials for late-stage, metastatic breast cancer and melanoma patients showed promising outcomes. We are working for US FDA approval of the modality for clinical trials in the US.

Laser-tissue photothermal interactions

We are conducting experiments to determine the temperature distributions in both tissue and gel phantom due to laser irradiation, as well as tissue responses under photothermal stimulation, to provide optimal parameters and procedures for laser immunotherapy.

Magnetic resonance imaging (MRI) guided laser cancer treatment

My research group is collaborating with the researchers at the Oklahoma Medical Research Foundation to develop an imaging guided laser treatment modality for cancers. We use MRI to detect the tumor and to monitor the tissue temperature distribution and tumor responses during and after laser immunotherapy treatment.

Laser–nanotechnology in cancer treatment

My research group is currently investigating laser-nanotube induced photothermal and biological reactions, using a novel immunologically modified single-walled carbon nanotube. This research could lead to a new way of treating tumors using laser and nanotechnology.

Interstitial laser immunotherapy

To effectively treat deep tumors, my research group is developing a new approach: Interstitial Laser Immunotherapy for metastatic cancers. This new approach is built upon our previous non-invasive laser immunotherapy. By using a cylindrical, side-fire optical fiber, we can insert the active fiber tip into deep tumors. This research could lead to a new clinical protocol for patients with deep tumors or tumors in internal organs.

High intensity focused ultrasound (HIFU) and immunostimulation in cancer treatment

We are developing a new cancer treatment modality using HIFU and a novel immunoadjuvant, glycated chitosan (GC). Our experimental results indicated that GC-HIFU could prevent or slow tumor metastasis in animals. This research could lead to a more effective cancer treatment modality.

Marshall Cheney, PhD

Marshall Cheney is an Assistant Professor in Health and Exercise Science at the University of Oklahoma. She received her B.A. in Psychology from Rhodes College and her M.A. in Psychology of Aging from Washington University in St. Louis. She received her Ph.D. in Health Promotion Sciences from the University of Oklahoma Health Sciences Center College of Public Health in 2010.

Dr. Cheney's research focuses on tobacco use in young adults. Before coming to OU, Dr. Cheney spent 14 years working in local public health administration at the Oklahoma City-County Health Department where she oversaw health promotion program design, implementation, and evaluation for Oklahoma County.

Jun Chung, PhD

Associate Professor in the Department of Neurology at OU Health Sciences Center

Major area of interest:

Dr. Jun Chung's research program is studying mechanisms of tumor cell invasion and metastasis, with a specific focus on the adhesion receptor integrin. While many integrins contribute to cancer progression, Dr. Chung's group is particularly interested in alpha6beta4 integrin, which has been implicated in breast, pancreatic and ovarian cancer progression. While alpha6beta4 integrin serves as an adhesion receptor for most of the known laminins in normal epithelial cells, this integrin switches its function as a signaling receptor to fuel invasion and metastasis in aggressive carcinoma cells. By using biochemical, molecular biological and cell biological tools, Dr. Chung's group aims to dissect the mechanisms how aggressive carcinoma cells switch the function of this integrin into a signaling receptor, which is a key event for invasion and metastasis. Recently, Dr. Chung's group identified the novel tumor suppressor gene called ARRDC3 which negatively regulates signaling function of alpha6beta4 integrin. The long term goal is to establish novel therapeutic strategies by targeting this integrin for currently untreatable sub-types of breast, pancreatic and ovarian cancers.

Education and Professional Experience:

1991	Yonsei University, Korea, B.S.
1992-4	University of Minnesota, Minneapolis, MN, M.S.
1994-1999	Washington University School of Medicine, St. Louis, MO, Ph.D.
2000-2005	Harvard Medical School, Boston, MA, Research Associate
2005-2011	LSU Health Sciences Center, Shreveport, LA, Assistant Professor
2011-2013	LSU Health Sciences Center, Shreveport, LA, Associate Professor
2013-present	OU Health Sciences Center and Peggy and Charles Stephenson Cancer Center, Oklahoma City, OK, Associate Professor

Wei-Qun Ding, PhD

Associate Professor, Member of the Stephenson Cancer Center
Department of Pathology, College of Medicine, OUHSC

RESEARCH INTERESTS: Novel mechanisms of n-3 polyunsaturated fatty acids' anticancer action; metal binding compounds as anticancer agents; microRNA regulation of gene expression in cancer cells.

This laboratory investigates the cellular and molecular mechanisms of actions of anti-cancer compounds with a long-term goal of developing novel strategies and effective agents for cancer treatment. In particular, we are interested in the actions of two types of anti-cancer agents: metal binding compounds and n-3 polyunsaturated fatty acids. A combination of cellular, molecular, and biochemical approaches are applied to address critical questions in our *in vitro* and *in vivo* model systems.

We also investigate gene expression regulation in cancer cells, with our current effort focusing on microRNA regulation of antioxidant enzyme expression, which is directly relevant to the development of novel anticancer strategies.

J. Kimble Frazer, MD, PhD

My lab uses zebrafish as a genetic model organism to study T cell malignancy. We investigate T cell cancer-prone mutant zebrafish lines to learn the genomic, genetic, and gene expression patterns that are oncogenic in T cell lymphoblastic lymphoma (T-LBL) and T cell acute lymphoblastic leukemia (T-ALL). Our projects aim to find new genetic mutations and molecular pathways that predispose vertebrates (zebrafish and humans) to T cell cancer. We also use zebrafish with cancer to test candidate compounds for T cell malignancy treatment.

Zebrafish (*Danio rerio*) are an emerging model system to study lymphocyte cancers. Nearly all *D. rerio* genes have human homologues with conserved molecular functions. Like people, zebrafish develop T cell cancers like T-LBL and T-ALL, and the genes responsible for human and *D. rerio* T cell cancers are the same. Like human T-LBL and T-ALL, the *D. rerio* versions of these diseases frequently originate in the thymus or spread to the thymus, forming tumors. Since the molecular causes of T-LBL and T-ALL are poorly understood, zebrafish provide a system to investigate the 'explanations' for these diseases. Also, because *D. rerio* cancers often regress after treatment with the same medicines used to treat human T-LBL / T-ALL, zebrafish can reveal the genetic reasons why some cancers respond to therapy but others do not. My lab conducts several projects based on using zebrafish models to learn more about human lymphocytic cancers:

- 1. Cancer-prone mutant fish:** We created 3 mutants, *hlk*, *otg*, and *srk*, with germline mutations that cause T cell cancer. We are mapping these unknown mutations to learn how they mediate cancer predisposition. We are also using microarray profiles and RNA-seq to decipher the molecular pathways that are perturbed by these heritable mutations.
- 2. Candidate oncogenes, tumor suppressors, and tumor progressors:** T cell cancers in fish suggest several genes of interest: *id3* and *osr2* (putative tumor suppressors), *tcf3* (a candidate proto-oncogene), and *c7orf60* (a potential tumor progression factor), among others. We are now studying these genes in greater detail.
- 3. An Oncogenic Retrovirus:** We discovered a retrovirus, ZFERV, which is amplified and over-expressed by *D. rerio* T cells and T cell cancers. We are testing if ZFERV is an insertional mutagen, like related retroviruses, or if it has other oncogenic properties.
- 4. Pre-Clinical Drug Testing:** Using fish with T-ALL / T-LBL, we are testing novel anti-neoplastic compounds to determine whether they are active *in vivo* against vertebrate T cell cancer.
- 5. Creating a New Cancer Model:** We are building transgenic zebrafish with B cell-specific expression of human *MYC*. This is designed to generate a new vertebrate model of Burkitt lymphoma, a cancer driven by *IgH-MYC* and *IgL-MYC* translocations.

Lucila Garcia-Contreras, PhD

Research Summary

The main interest of my laboratory is the targeted delivery of drugs encompassing development of novel formulations, physicochemical and in vitro characterization and evaluation of such formulations, pharmacokinetic and pharmacodynamics evaluation. Even though our primary focus is Pulmonary Drug Delivery, we have experience in other routes of administration and dosage forms. These include oral, transdermal, nasal and implants. Our laboratory is capable of developing formulations for a specific route to be administered by most routes. We have experience in developing analytical methods for drug determination in biological matrices (plasma and tissues) and can perform pharmacokinetic studies in laboratory animal models. We are one of 4 sites in the US to have the guinea pig model of tuberculosis well established for the testing of novel drugs and vaccines. Overall, our goal is to design therapies that are more efficient and more convenient in delivering therapeutic or prophylactic agents to the site of action, thereby maximizing efficacy and efficiency of the agent and minimizing its undesired side effects.

My research objectives are encompassed in the following four areas:

1. To study mechanisms of drug transport in the lung in order to maximize delivery strategies;
2. To optimize currently proposed therapies for the treatment of pulmonary diseases such as tuberculosis and cystic fibrosis;
3. To understand the mechanisms of immunogenicity and protection when vaccines are administered by the pulmonary route; and
4. To design more effective therapies for the treatment of lung cancer.

Current funded projects on my laboratory are:

- Development, formulation and evaluation of a powder vaccine against West Nile Virus for nasal administration.
- Pharmacokinetics of a novel anti-tuberculosis drug
- *In vitro* evaluation of novel anti-tuberculosis compounds
- Development, formulation and evaluation of a handful novel anti-cancer compounds
- Mechanistic studies of inhaled vaccines against tuberculosis

Gary Gorbsky, PhD

The several ongoing projects in the Gorbsky laboratory focus on understanding cell division (mitosis and cytokinesis) in vertebrate cells, both normal cells and cancer cells. One complex signaling pathway, termed the metaphase checkpoint (or the mitotic spindle checkpoint), promotes the equal segregation of chromosomes by blocking their separation at anaphase until all are properly aligned at the metaphase plate. Defects in this pathway during mitosis contribute to the development of cancer. In cancer cells, the metaphase checkpoint system is often faulty, leading to the generation of cells with too many or too few chromosomes. The resulting imbalances in gene dosage and the loss of normal gene alleles can generate aberrant cells with malignant and metastatic characteristics.

We have discovered that the metaphase checkpoint is regulated by a mechanical signal. This signal is generated at the kinetochore, the specialized region of the mitotic chromosome that attaches to the spindle microtubules. The metaphase checkpoint is regulated by the mechanical stretching of the kinetochore region as it attaches to the mitotic spindle. Only when all the chromosomes are attached and aligned is the signal turned off and the chromosomes allowed to separate. Thus a single unattached chromosome can block the segregation of all the others. The creation, transmittal and regulation of the metaphase checkpoint signal involve a remarkably complex degree of protein trafficking regulated by mechanical tension at the kinetochores. We use advanced techniques of fluorescence microscopy as well as modern approaches in molecular biology and biochemistry to study the functional interactions of these proteins in isolation or in extracts prepared from mitotic cells.

Defects in the metaphase checkpoint clearly contribute to the advancing malignancy of a developing cancer. However, paradoxically these same defects may render them more susceptible than normal cells to treatment with certain classes of therapeutic anti-cancer agents. To improve the therapeutic efficiency of these anti-cancer agents, we are using high-throughput assays to screen libraries of small chemical compounds. Our goals are to develop drugs that specifically target components of the spindle checkpoint pathway. These drugs may one day be used in anti-cancer therapy. We have achieved the ability to control and even reverse the events of mitotic exit, something previously thought impossible. These studies will aid in understanding basic cell cycle control mechanisms that operate to control division of normal and malignant cells.

Lastly, we are using bioinformatics to find and characterize novel regulators of vertebrate cell cycle control and chromosome movement in mitosis and cytokinesis. The results of these studies are identifying new pathways that regulate cell division. These new pathways may be hyperactive in cancer cells and thus provide novel avenues for anti-cancer therapy.

Roger G. Harrison, PhD

Professor, Bioengineering Program and School of Chemical, Biological and Materials Engineering
University of Oklahoma Norman, Oklahoma

Roger G. Harrison received his B.S. degree in chemical engineering from the University of Oklahoma and his M.S. and Ph.D. degrees in chemical engineering from the University of Wisconsin-Madison. Before joining the School of Chemical, Biological and Materials Engineering at the University of Oklahoma in 1988, he worked for six years in the Fermentation Research and Development Department at the Upjohn Company in Kalamazoo, Michigan, and for seven years in the Biotechnology Division at the Research Center of Phillips Petroleum Company in Bartlesville, Oklahoma. He is first author with three coauthors of the textbook *Bioseparations Science and Engineering* (Oxford University Press, 2003), which has been adopted for courses at over 60 universities throughout the world. The major areas of his research interest are the development of novel enzyme prodrug therapies for treating solid tumors and the targeting of nanoparticles, particularly single-walled carbon nanotubes, for treating tumors using photothermal therapy. He has studied treatments for breast, pancreatic, prostate, and lung cancer.

Lewis Hassell, MD

Principle Investigator's Research Interest

Dr. Lewis Hassell is the director of anatomic pathology in University of Oklahoma Health Sciences Center Department of Pathology. The primary research interests of Dr. Hassell are in the area of utilizing modern technology and concepts in clinicopathological diagnoses of diseases. At the same time, his interests also include process improvements, error reduction and quality gains in laboratory workflow, and structural and organizational alignment for optimization of work teams in a variety of medical environments. He is also interested in ways of applying process improvement to enhance access to care, and specifically pathology services, to underserved populations domestically and internationally. The interface of current status quo with potentially disruptive technology or processes, and how to use these fault lines to open up access rather than restrict it are challenges he is working on solving.

Michael A. Ihnat, Ph.D.

Department of Pharmaceutical Sciences
University of Oklahoma College of Pharmacy

Research Overview

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.

Michelle Hopkins, BS

Michelle Hopkins is the Field Coordinator for the All Nations Breath of Life research study. Ms. Hopkins has 18 years of experience as a research coordinator with over 10 years of experience working with American Indian communities in the areas of diabetes, cancer and tobacco cessation.

Shirley James

Shirley James' principle area of interest is tobacco control research. She is interested in observational as well as clinical trial research.

Naveena Janakiram, PhD

My primary area of research interest is in the colon and pancreatic cancers. Majorly my area of research is the identification of natural and chemical agents that exhibit tumor inhibitory efficacy in these cancers. I study the mechanisms involved with immune modulation by novel agents in cancer inhibition. As well, I specifically study the role of CD4⁺, CD25⁺, FOXP3 T regulatory and Natural Killer (NK) cells during colon carcinogenesis. Further my research involves to elucidate how these immune cells interact in enhancing or suppressing stem like cells in colon cancer development. This basic research results will help to design or identify the agents which can modulate these immune cells to inhibit cancer development or to restrict the cancer progression. I am Assistant Professor of Research in the Medicine Department of Hem/Onc and working with Dr. Chinthalapally Rao at Center for Cancer Prevention and Drug Development.

Ralf Janknecht, PhD

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.

Melanie Johnson, MEd

Melanie is the Research Project Coordinator for the All Nations Breath of Life (ANBL) research study. Ms. Johnson has 9 years of community-based experience as a Research Project Coordinator working closely with American Indian communities focused on diabetes, heart disease and tobacco prevention programs.

Rashmi Kaul, PhD

Research Interest Description:

My laboratory investigates the role of estrogen and estrogen receptors in regulation of immunity and inflammation during infectious disease development or chronic infectious disease induced cancer development. We are working on two major projects studying modulation of hormones and their receptors in disease pathogenesis.

We are studying the estrogen related etiology of *Hepatitis C virus* (HCV)-related cirrhosis leading to cancer development. HCV infection is the prime cause of rising incidence of Hepatoatocellular 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 research 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* and *in vivo* disease models to understand estrogen and estrogen receptor regulated modulation of HCV -related carcinogenesis.

Our long term goal in the lab is to understand the molecular mechanisms of estrogen related regulation of immunity, inflammation and immune regulation during host pathogen interaction and pathways related to cancer development.

David Lam, MD

David Lam is currently a third year hematology/oncology fellow here at the Stephenson Cancer Center. Prior to starting his fellowship he completed his residency in Internal Medicine in 2010 also here at the OUHSC, where he was also Chief Medical Resident. He is currently working with Dr. Mohamad Cherry on creating a prospective registry of patients treated for leukemia at the OU Medical Center.

Fritz Laux, PhD

The main focus of Dr. Laux's research has been on the logic of cost-benefit analysis as it is applied to topics in tobacco regulation. This includes the Laux (2000) argument that the rational addiction model can be viewed as a null hypothesis for a hypothesis test of the assumption that the smoker's choice to take up and continue smoking is a rational one. The implication from rejecting this null hypothesis is that the primary reason we regulate cigarettes should be to address the externality that young smokers impose on their future selves ("internality" as a market failure). Laux and Peck (2009) reviewed the growing literature on this issue of "internalities," further evidence for inconsistency in consumer choice, and the hyperbolic discounting model that has emerged as the leading alternative to the "rational" or exponential discounting model that economists normally use. Laux continues to work on arguments for how to structure cost-benefit analyses so that these analyses can take the inconsistency of the choice behavior of individual consumers into account. In related work, Laux has participated in a project lead by Geoffrey Fong that looked at the near universal extent to which smokers regret having become smokers. He has also worked with Andrew Hyland and the International Tobacco Control (ITC) survey project looking at the price shopping behavior of cigarette smokers.

Laux's current research on Oklahoma topics has involved an ongoing activity to track the pricing behavior of commercial and tribal smoke shops in the state. These data can be used to evaluate the cross-tribal revenue impact of changes in tribal tax rates, changes in tax treaties, and changes in pricing policy. Laux is also available for any assistance or analysis work he can provide for the Oklahoma State Department of Health, such as in the analysis of smoking bans and Oklahoma's current pre-emption law.

William V. Lechner, MS

Oklahoma State University

Oklahoma Tobacco Research Center (OTRC)

William is a fifth-year graduate student whose primary interests involve examining the relationship between anxiety and addiction. He is particularly interested in utilizing psychophysiological techniques (e.g., affective modulation of the startle response) to examine this area of research. His master's thesis examined the influence of stress and anxiety on the modulation of the startle response to drug cues in a nicotine dependent sample. More recently, he has been studying the relationship between psychopathology and addiction in an inpatient drug treatment center in Washington, D.C. Additionally, he has been involved with the Marketing Department in an ongoing study examining trends in drug use on the OSU campus.

Patrick McCann, PhD

Research Interests

A goal of my research group is to develop sensors that can measure gas phase biomarkers associated with cancer. This work involves fabrication of mid-infrared laser spectrometers designed for detection of trace concentrations of specific gas phase molecules in exhaled breath. My group has pioneered the application of mid-IR laser technology for medical diagnostic applications. Prior work showed that it is possible to perform real-time detection of exhaled nitric oxide (eNO) in exhaled breath with sensitivities of better than 1 ppb, a capability that enables the assessment of the airway inflammation that afflicts asthma patients. Based on this past success, my group is now focused on developing laser-based sensors for detecting cancer. This effort is inspired by the multiple recent demonstrations of accurate detection of cancer by canine olfaction. It is further guided by the understanding of the biochemical processes associated with the altered metabolism of cancer cells (i.e. Warburg effect). My group has put forward the hypothesis that higher pyruvate concentrations in cancerous cells, a Warburg effect phenomenon, results in higher acetaldehyde concentrations due to a non-catalyzed exothermic degradation reaction. In prior published work, my group has shown that mid-IR laser technology can be used to perform sensitive measurement of acetaldehyde in exhaled breath. However, the hardware used in this prior work was not suitable for use in clinical settings. Future work by my group is therefore now focused on developing improved mid-IR laser spectroscopy hardware so that further clinical work on validating acetaldehyde and other gas phase molecules as biomarkers for cancer.

Ellen Meier, M.S

Ellen Meier, M.S. is a 4th year Clinical Psychology doctoral student at Oklahoma State University. As an OTRC Summer Scholar she completed several projects examining general tobacco use and e-cigarettes among community members and at “vape” or e-cigarette stores. She also served as an interventionist for two tobacco cessation studies, one in a sample of women diagnosed with cervical dysplasia, and another in a sample of young adults attending smoke-free bar nights. She is currently pursuing a predoctoral internship with a focus in health psychology. Following internship, she plans to pursue a postdoctoral fellowship to gain additional research experience with populations at risk for tobacco use as well as effective tobacco cessation interventions.

Blaine Mooers, PhD

Department of Biochemistry and Molecular Biology
Stephenson Cancer Center

Our lab is interested in the role of RNA structure in biomedicine. We are particularly interested in systems involving small trans-acting RNAs that bind antiparallel to messenger RNA and direct the cleavage of the mRNA. We are funded by the NIH to study one such system that directs the insertion and deletion of uridylates at over 2300 sites in mitochondrial RNA in trypanosomes. The goal of the work is to obtain structures of RNA and proteins involved in RNA editing for the design of better drugs. We have had success at crystallizing a number of double-stranded RNA fragments from this system. We have also collected small angle X-ray scattering (SAXS) on these RNAs in solution. This latter method gives low-resolution (~ 10 Å) data about the overall shape of the molecule in the absence of crystal packing contacts. SAXS has the advantage of not requiring crystals, so sample preparation is faster. We collect our initial X-ray diffraction data with the in-house instrument in the OUHSC Department of Biochemistry and Molecular Biology's X-ray Crystallography Lab. These in-house data can be of high quality, and we have published some of it recently. However, we often collect the final data for publication using synchrotron radiation at national labs. We currently lack a small-angle X-ray scattering instrument and have to use the instruments at national labs. Access to the latter instruments is extremely competitive.

In the past several years, I have broaden the scope of our research program to include structural biology projects related to cancer and in particular to those with overlapping interests in nucleic acid-protein interactions (hJMJD) or structure-based drug design (hGGT). I am the PI on the on the crystallographic studies of JMJD4 from the family of human JMJD proteins—histone modifying proteins that demethylate lysines or arginines in histones and other proteins and that are thought to be oncoproteins or tumor suppressors. This work is being done in collaboration with Dr. Ralf Janknecht, Cell Biology, OUHSC. Second, my lab published the first crystal structure of human gamma glutamyl transferase (GGT) in October of 2013. This membrane bound protein is involved in glutathionine metabolism. Its inhibition in tumor cells has the promise of making those cells more sensitive to chemotherapy. This work was done in collaboration with Dr. Marie Hanigan, Cell Biology, OUHSC. Her lab is carrying this work forward by doing structural studies of inhibitor complexes.

Dana S. Mowls, MPH

I am currently a PhD student with the Department of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center. Motivated by my graduate research assistantship with the Biostatistics Epidemiology Research Design and Analysis Center (BESRDAC), I have developed research interests in cancer epidemiology and tobacco control and prevention. In particular, I am interested in applying epidemiologic methods to studying cancer disparities that are driven by tobacco and/or nicotine use and other lifestyle behaviors. I hope that my research will contribute to the field of science that works to reduce the burden of cancer and increase long-term survivorship.

Priyabrata Mukherjee, PhD

One of the major focus of Prof. Mukherjee's research is in delineating the role of metabolic enzymes in cancer progression and angiogenesis. His research also focuses on the understanding of the basic principles of cell-nanomaterial interaction as a way to discover new molecular targets and signaling events in various malignancies.

Principal Investigator's research interests:

The research of Priyabrata Mukherjee, Ph.D., focuses on understanding the basic principles of cell-nanomaterial interaction as a way to discover new molecular targets and signaling events in various malignancies. This multidisciplinary field spans the disciplines of biology, chemistry, materials science, engineering and medicine.

- 1. Anti-angiogenic property of inorganic nanomaterials.** Dr. Mukherjee and his team, for the first time, demonstrated the anti-angiogenic property of gold nanoparticles. Gold nanoparticles bind heparin-binding growth factors and thereby inhibit their function. Dr. Mukherjee is now working on determining the mechanism of interaction to design a better strategy to combat ovarian cancer.
- 2. Overcoming drug resistance.** Using nanotechnology, Dr. Mukherjee and his team are developing a unique method to overcome the resistance of traditional chemotherapeutics, such as cisplatin and gemcitabine.
- 3. Nanoendocytosis.** Dr. Mukherjee's group is involved in understanding the basic mechanism of cellular entry of nanomaterials, as well as switching the targeting pathway as a means to target specific cellular process and identify adapter molecules involved in the process of endocytosis of nanomaterials.
- 4. Identification of new molecular targets.** Dr. Mukherjee and his colleagues use surface-engineered gold nanoparticles to detect otherwise undetected proteins (in other words, visualizing invisible proteins) as a way to determine new molecular signatures and therapeutic targets in cancer. They use a combination of nanotechnology, proteomics and bioinformatics analysis to identify new therapeutic targets.
- 5. Metabolic enzymes in cancer.** Dr. Mukherjee and his team are involved in determining the roles of metabolic enzymes in cancer.

Anupama Munshi, PhD

My research is focused on understanding the specific molecular mechanisms and biological processes that govern tumor response to radiation and other anticancer agents. A major emphasis of my research has been on developing innovative and effective approaches to sensitize tumor cells to radiation and DNA damage and studying the molecular mechanisms of resistance to radiation-induced tumor cell death.

One area of research in my lab is focused on studying the molecular mechanisms by which estrogen receptor expression is regulated in breast cancer and developing strategies to restore estrogen expression in breast cancer. In addition we are carrying out studies to correlate the loss of estrogen receptor and development of radiation resistance. My research has demonstrated that both HDAC inhibitors and demethylating agents can independently restore radiosensitivity to breast cancer cells that lack estrogen receptor by reactivating estrogen receptor. More recently we have been evaluating the interaction between the signaling molecule, ERK, and DNA repair machinery as a basis for the radioresistant phenotype seen in ER-negative breast cancer cells. The results from this study should help define the interaction between estrogen receptor and ERK-mediated molecular signaling in radioresistant breast cancer cells. A more recent area of research in my lab is centered around investigating the role of epithelial to mesenchymal transition (EMT) in radiation resistance of human breast cancer. We anticipate that the answers to the questions raised above will help discover strategies that could be used to modulate EMT, thereby restoring radiosensitivity, and ultimately impact the treatment of breast cancer patients. In addition we would like to develop a predictor model that identifies proteins linked to failure after radiation.

Augen Pioszak, PhD

Assistant Professor
Biochemistry and Molecular Biology
OUHSC

Research Interests:

Structural biology of cell surface receptors and their ligands; molecular mechanisms of G protein-coupled receptor signaling; structure-based development of therapeutic agents.

Our research is aimed at understanding the structure and function of cell surface receptor/ligand complexes involved in clinically important cellular signaling pathways. We are currently focused on G protein-coupled receptors (GPCRs), a class of proteins that is responsible for mediating the actions of many peptide and protein hormones, neurotransmitters, and various other bioactive molecules. GPCRs constitute the largest family of cell surface signaling proteins in the human genome and they are among the most successful targets for therapeutic intervention with about 40% of drugs on the market targeting GPCRs. Despite their physiological and clinical importance, many fundamental questions about GPCR function remain unanswered. How do endogenous ligands and drugs bind to the receptor and how is specificity/selectivity achieved? How are signals transduced across the membrane? How do additional regulatory proteins interact with the receptors and modulate their function?

We use a multi-disciplinary approach to try to answer these questions. Our primary tool is X-ray crystallography for structural studies, but we also employ the tools of biochemistry, pharmacology, and cell biology for functional studies. A major project in the lab is centered on structure/function studies of a subset of GPCRs known as class B receptors. This class of GPCRs includes the receptors for parathyroid hormone, calcitonin, glucagon, corticotropin releasing factor, adrenomedullin, and several other clinically important endocrine hormones, autocrine/paracrine factors, and neuropeptides. A second project in the lab seeks to understand how R-spondin adult stem cell growth factors modulate the Wnt/ β -catenin pathway by signaling through two classes of cell surface receptors: the class A GPCRs LGR4, -5, and -6, and the transmembrane E3 ubiquitin ligases ZNRF3 and RNF43. Our efforts are focused on four areas: (a) expression and purification of ligands and soluble domains of the receptors, (b) expression and purification of full-length receptors, (c) structural studies of receptor/ligand complexes using X-ray crystallography, and (d) functional studies using purified proteins and cell-based assays of receptors in their native membrane environment. Ultimately, we plan to use the knowledge gained from our studies to guide the design of therapeutic agents targeting these receptors for the treatment of diseases including osteoporosis, depression, diabetes, and cancer.

Lurdes Queimado, MD, PhD

I am an Associate Professor in the Departments of Otorhinolaryngology, Cell Biology and Pediatrics, and the Director of Basic and Translational Research in the Department of Otorhinolaryngology at the University of Oklahoma Health Sciences Center. I hold an endowed professorship, the Presbyterian Health Foundation Chair in Otorhinolaryngology, and my research has been continuously funded since 2004 by local and national institutions. I have established a large head and neck tissue bank, as well as several unique and rare normal and tumor cell lines, which have been distributed all over the world. The recognition of my expertise in salivary gland oncology by the scientific community led to my contract as a consultant for the National Salivary Gland Tumor and Cell Line Biorepository, and my participation in a NIH think tank workshop in 2012 to define the “Current Status and Future Directions in Salivary Gland Tumor Research”. 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, chemotherapy and radiotherapy 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 by developing a novel and highly sensitive assay (PADDa) to map and quantify *in vivo* levels of DNA damage. Using PADDa, we have mapped for the first time highly mutagenic nucleotide lesions *in vivo*. PADDa is the only available assay able to map and quantify DNA damage caused by the endogenous metabolism, and has higher sensitivity than other available assays to quantify DNA damage induced by exogenous agents. PADDa's high sensitivity and simplicity makes it the first DNA damage detection assay practical for population screening. We are currently exploring the utility of this assay for cancer risk stratification among smokers in diverse populations, and the prediction of head and neck cancer risk and response to chemotherapy.

2. Role of Wnt/ β -catenin Signaling Pathway in Oncogenesis and Cancer Treatment:

The Wnt/ β -catenin signaling pathway plays crucial roles in embryogenesis and adult tissue homeostasis. We have demonstrated that aberrant activation of β -catenin contributes to head and neck, salivary gland and cervical cancers. Most importantly, we established WIF1, a major inhibitor of the Wnt pathway blocks tumor growth through distinct mechanisms that differ significantly in different tumor types. Presently, we are particularly interested in the molecular mechanisms that regulate normal and cancer stem cell self-renewal and multi-potency. We are also characterizing the specific mechanism of action of Wnt proteins, and determining whether Wnt inhibitors are potential cancer therapeutic agents. Our studies offer new insights into the regulation of the Wnt pathway and have documented the therapeutic potential of specific Wnt pathway inhibitors. Our ultimate goal is to develop novel drugs to combat cancer and to minimize major side-effects of current treatments.

Rajagopal Ramesh, PhD

Professor, Jim and Christy Everest Endowed Chair in Cancer Developmental Therapeutics,
Department of Pathology, The University of Oklahoma Health Sciences Center

Treatment of lung cancer remains a major challenge in the USA and around the world. The five-year survival rate is dismal (14%) and has not significantly improved despite advances made for lung cancer therapy. Therefore, development and testing of novel therapeutic strategies are needed.

Studies in our laboratory are focused in developing and testing various formulations as gene and drug delivery vehicles for systemic treatment of cancer and have successfully been translated into clinical testing for treatment of solid tumors including lung cancer. Additionally, our laboratory is investigating the antitumor activities of novel tumor suppressor genes and small molecule inhibitors.

Ashish Ranjan, B.V.Sc. (DVM equivalent), Ph.D

Assistant professor in the Department of Physiological Sciences, Center for Veterinary Health Sciences at Oklahoma State University.

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 selectively accumulate tumors, permitting enhanced 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, impeding or preventing distribution to poorly-perfused remote cells in the tumor core that contribute to drug resistance and tumor recurrence. Thus the tumor-directed dose escalations achieved to date via stealth liposome technology have not yet improved treatment efficacy. 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 liposomal drug release using mild local elevations in tissue temperature, and their application in combination with devices such as 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, rather than accumulating at tumor sites, 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 (PBRT) with drug encapsulated nanoparticles to achieve radiation triggered delivery of anticancer agent at the targeted site

Carol Rogers, PhD, RN

Assistant Professor OUCN

Statement of Principal Investigator's Research Interests

I am interested in promoting physical activity to maintain physical function, quality of life, and independence in older adults and persons with chronic disease including cancer I was an active member of a research team that tested the effect of a Tai Chi/Qigong exercise compared to a non-meditative exercise on fatigue, sleep, cognition, and BMI among breast cancer survivors. The findings of that research have been reported at local, state, and national research conferences and a manuscript is under review for publication with the *Journal of the National Cancer Institute*.

I plan to use the data collected in this study as a foundation to: (a) generate a minimum of two publications in high quality, peer-reviewed journals; and (b) support preparation of an R01 competitive grant application to conduct a larger RCT testing the effect of the adapted SCD intervention on cancer related fatigue and sleep among women during treatment for breast cancer.

Heather M. Ross, MPH

My research interest focuses on community based tobacco control and prevention work, and systems approaches to tobacco cessation. Specifically, I am interested in identifying strategies, organizational competencies, environmental factors, and individual characteristics associated with successful tobacco control policy advocacy and systems level change. Recently, my work has focused on youth involvement in tobacco control policy initiatives. I am interested not only in how and when they are most effective, but also in how youth advocates can be trained most effectively, how their involvement in tobacco control advocacy activities can be sustained, and in ways to identify both their tangible and intangible contributions to adult tobacco control coalitions.

David Schmidtke, PhD

Dr. Schmidtke carries out research in the areas of bioelectrocatalysis, cell adhesion, and micro/nanofabrication. In the area of bioelectrocatalysis, Dr. Schmidtke's group uses redox polymers to electrically "wire" the redox centers of enzymes to electrode surfaces for both biosensing and miniature biofuel cell applications, and employs the unique properties of single-walled carbon nanotubes to fabricate novel nanoscale biosensors. Dr. Schmidtke's research interests in cell adhesion have focused on developing high resolution/high speed imaging techniques as well as micro- and nano-scale protein patterning methods for studying the biomechanics and biophysics of platelet, leukocyte, and cancer cell adhesion under flow.

W. Kyle Simmons, PhD

Dr. W. Kyle Simmons' research interest lies in understanding the neural systems underlying the conceptual representation of reward and interoception in humans. Currently, his 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, his lab is undertaking studies of interoception and reward inference in cigarette smokers, to clarify the role of interoceptive regions in the insula in the neural basis of nicotine craving. The motivation for his lab's studies with smokers is the hope that by understanding at the neural level how interoception and nicotine craving work to potentiate nicotine rewards, we can identify central nervous system mechanisms influencing tobacco-use and the success of smoking cessation interventions.

In an associated area of research, Dr. Simmons' lab is examining the functional organization of the insula 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 his 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. These two domains of research are in fact highly related, as the insula plays an important role in food motivation and gustatory representation, and interoception is an important component in satiety signaling.

The common goal of the various lines of research in Dr. Simmons' lab is to elucidate how the body's homeostatic state influences reward representation and its related decision-making, both normatively as well as in psychiatric illness and substance abuse disorders.

Grant H. Skrepnek, PhD

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 broader economic and health policy concerns across several types of cancers and other disease states. His contributions to research teams has included funding by the NCI (National Cancer Institute), AHRQ (Agency for Healthcare Research and Quality), and PCORI (Patient-Centered Outcomes Research Institute), among numerous other public and private organizations.

Tracey Strader, MSW

Tracey Strader became the first Executive Director for the Oklahoma Tobacco Settlement Endowment Trust in August 2002. She holds a master's degree in social work, and is licensed by the State of Oklahoma. Strader has broad experience in providing direct services, management and administrative oversight for community-based and statewide programs. For nearly 30 years, she has been extensively involved in the design, implementation, and evaluation of programs related to public health, tobacco control, maternal and child health, services for senior adults, and mental health and substance abuse services.

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.

Kristina Suorsa, MS

Kristina Suorsa, M.S. is a third year graduate student in the clinical psychology PhD program at Oklahoma State University (OSU) under the mentorship of Larry L. Mullins, Ph.D. Kristina attended the University of Rhode Island, graduating with a B.A. in psychology and French. Before attending OSU, Kristina worked for three years at Hasbro Children's Hospital, completing research in adherence with children and adolescents with inflammatory bowel disease. Kristina's current research interests include the use of electronic monitoring devices to improve health behaviors. In addition to her work at OSU, Kristina is a graduate research assistant at OU Health Sciences Center, working with families of children with cancer in Hematology/Oncology to better understand parental stress. She also works with Dr. Stephen Gillaspay to reduce second hand smoke exposure in primary care patients. Upon graduation, Kristina would like to continue her research to improve health behaviors in an academic medical center.

Takemi Tanaka, PhD

My laboratory's central theme is the development of a framework for personalized medicine for the prevention of breast cancer metastasis. Current personalized medicine focuses on the acquisition of genetic information, the discovery of new molecular targets, and biomarker discovery for patient selection. My view of personalization includes drug development, drug selection, and prospective clinical care. This central theme is further divided into three major project lines: 1) development of a novel anti-adhesion therapy for the prevention of breast cancer metastases, 2) identification of CTC biomarker in for the prediction of organ metastasis, 3) development of humanized mouse model for breast cancer.

In the era of personalized medicine, targeted therapy has increased in cancer therapy. For the realization of personalized medicine, the developments of new therapeutic strategies that enable targeted tumor components with superior selectivity with minimum toxicity are an absolute necessity. My laboratory has developed a therapeutic strategy to target the adhesion cascade to inhibit the adhesion of circulatory cells to the vascular endothelium and subsequent tissue migration. This strategy stems from the vision that the vascular endothelium function as a gateway for all circulatory cells for their tissue entry. Effective blockade of the adhesion cascade is expected to inhibit the tissue infiltration of circulating metastatic cancer cells, which will subsequently inhibit the development of metastatic niche.

In paralleled with environmental cue to support the tissue entry of circulating cancer cells, my laboratory also focus on the circulating tumor cells (CTC). During hematogenous metastasis only a small subpopulation of circulating tumor cells (CTC) survive in the circulation and successfully metastasize to the target organ, and therefore CTC is an excellent pool to obtain information regarding what types of CTC gives a rise to overt metastasis. My laboratory focus on the identification of biomarker present in CTC for the prediction of a risk of metastasis with an ultimate goal of monitoring patients longitudinally and initiate prospective therapy for women at high risk as necessary.

Rheal Towner, PhD

Dr. Towner is the Director of the Advanced Magnetic Resonance Center at OMRF, with extensive experience (over 26 years with over 100 refereed publications) in the use of MR techniques to assess pathophysiological processes in animal models for cancer (mainly focusing on gliomas and recently on pediatric gliomas), tissue injury, and inflammation. Dr. Towner has used and assessed various orthotopic, xenograft and transgenic models for tumor development in the past 16 years, and has incorporated MR imaging and spectroscopy methods to detect morphological, biophysical, functional and metabolic alterations associated with tumor growth, as well as assess therapeutic response. Another major focus in Dr. Towner's group has been the assessment of a novel anti-cancer agent, OKN-007, in gliomas which is currently an investigational drug for recurrent high-grade gliomas in a phase Ib/IIa clinical trial. Dr. Towner has also been involved in the development and assessment of molecular-targeted MR-visible probes for the assessment of *in vivo* levels of tumor growth and angiogenesis markers in pre-clinical models for cancers, including VEGFR2, c-Met, iNOS and free radicals (e.g. ROS).

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.

Ashley H. 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.

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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 Carolina 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.

Ming-Hui Zou, MD, PhD

Dr. Zou's ongoing research programs within the Section of Molecular Medicine include various disease models focusing on vascular biology. More specifically, Dr. Zou's laboratory examines the means to sense oxidative stress, reduce it, or ameliorate the body's adverse response to it. He has been instrumental in examining the role of nitric oxide and oxidative stress in the regulation of blood flow and vascular function. He performed elegant, state of the art, studies to show that the selective modification of two key proteins, prostacyclin synthase and endothelial nitric oxide synthase, is critical in the dysregulation of vessel function from nitric oxide and superoxide. Dr. Zou's research group was also the first to demonstrate that the AMP-activated kinase (AMPK), a key enzyme in the regulation of energy metabolism, obesity, diabetes, and cardiovascular diseases, functions as a sensor and regulator of oxidative stress. Dr. Zou's contributions in this area are important and his work represents outstanding breakthroughs in research which have been recognized by many other investigators in the fields. Dr. Zou is an independent investigator of the National Institutes of Health, American Diabetes Association, and the Juvenile Diabetes Research Foundation International (JDRF) and a recipient of Scientist Development Award (SDG) and National Established Investigator (EIA) Award of the American Heart Association. He has served on several national and international study panels such as the National Institutes of Health and American Heart Association. In 2008 he was elected to the American Society for Clinical Investigation, membership in which reflects accomplishments by its members at an early stage in their careers and one of the United States' oldest honor societies of physician-scientists.

Membership Program Information and Application

Membership Information

Cancer Center Membership

Membership in Stephenson Cancer Center is open to all faculty members from the University of Oklahoma or other eligible institution (see below) who will promote the mission and goals of the SCC. Members from all areas of cancer research are encouraged, including basic, translational and clinical research, pharmaceutical sciences, populations sciences, and behavioral and psychosocial science.

Who is Eligible for Membership?

- Faculty from the University of Oklahoma (Health Sciences Center, Norman or Tulsa campuses), Oklahoma Medical Research Foundation, Oklahoma State University or other affiliated institution who are actively engaged in cancer-related research
- OU Health Science Center clinical faculty from any discipline who are actively engaged in clinical research and patient care activities to better understand and treat cancer

Membership Benefits

- Research Funding – The SCC provides directed-research and seed grant funding opportunities to members to support promising cancer-focused projects.
- Program Membership – As a member of an SCC research program, members have access to activities and funding intended to promote and support program-focused, collaborative research.
- Shared Resources – The SCC has multiple shared resources to support cancer research. SCC members typically receive discounted rates at these shared resources.
- Research Seminars – The SCC hosts an active annual schedule of research seminars, workshops and events.
- Proposal Services Support – The SCC's Proposal Services Core can assist SCC members with grant preparation and submission.

Membership Categories

Member (Full): Faculty who are actively engaged in cancer research as evidenced by being:

- Principal Investigator on a national, peer-reviewed, cancer-focused grant, **or**
- Principal Investigator of a peer-reviewed, investigator-initiated, interventional clinical trial, **or**
- Holding a significant administrative or leadership position in the SCC

Associate Member:

- Faculty who are actively engaged in cancer-related research as evidenced by a record of peer-reviewed publications and / or grants, **or**
- Faculty from any clinical discipline who are actively engaged in clinical research and patient care activities to better understand and treat cancer

Research Program Affiliation

Applicants should select a Research Program that best aligns with their primary research interests:

- [Cancer Health Disparities Program](#)
- [Basic Cancer Biology Program](#)
- [Gynecologic Cancers Research Program](#)
- [Experimental Therapeutics Program](#)

Application and Appointment Process

A completed Membership Application Form along with *curriculum vitae* and an updated NIH biosketch should be submitted via email to:

Peggy and Charles Stephenson Cancer Center

Office of Cancer Research

Phone: 405-271-1878

Email: CancerResearch@ouhsc.edu

All applicants will receive a letter from the SCC notifying them of the decision concerning membership within 30 days of submitting a complete application. Membership appointments will be for three years.

Membership Review

Cancer Center membership will be reviewed every three years. Members will be asked to submit an updated NIH biosketch and a brief statement describing current research, interactions within their primary program, and any other pertinent information.

Membership categories may be reassigned, or membership may be revoked, if performance criteria are not met. The SCC Director has final authority pertaining to membership assignment and revocation.

Cancer Center Seed Grant Awardees

FY 2013 Seed Grant Awardees

MidFirst Breast Cancer Research Seed Grant

Thank you to MidFirst Bank whose generous gift has provided support for these seed grants.

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

Sign Chi Do and Expressive Writing for Breast Cancer Patients

Breast Cancer Clinical
Research Disease Site
Group
Wajeeha Razag, MD
(Group Chair)

Strategies to Enhance Identification, Screening and Participation of
High-Risk and Breast Cancer Patients on Interventional and
Observational Clinical Trials

TSET Cancer Research Program Research Support

Doris Benbrook, PhD and
Franklin Hays, PhD

Therapeutic Targeting of HSP70 Chaperones in Cancer Drug
Discovery

Rajagopal Ramesh, PhD
and David Schmidtke,
PhD

Exosomes and Tumor-Microenvironment Signaling in Response to
Therapy

Doris Benbrook, PhD and
Christopher West, PhD

Glycoprotein Analysis of Gynecologic Cancers

Sukyung Woo, PhD

Phase 0 Trial of NSC 726189 (SHetA2) in Patients with Dysplasia

Doris Benbrook, PhD, Rajagopal Ramesh, PhD, and Marie Hanigan, PhD	Ovarian Cancer Chemoresistance Subgroup
Jay Hanas, PhD Erin Bishop, MD	Uterine Cancer Study CCLD Cytokine in Co-Morbidities of Endometrial Cancer, Diabetes and Obesity
Blaine Mooers, PhD	Structural Studies of Human JMJD4 by X-ray Methods
Joe Zhao, PhD	The Role of p53 in JAK2V617F-Induced Myeloproliferative Neoplasms
Blas Espinoza-Varas, PhD	Executive-Control Deficits Induced by Adjuvant Ovarian-Cancer Chemotherapy
Melissa Craft, PhD, APRN, CNS, AOCN	The Experience of Cancer in American Indians Living in Oklahoma
Ralf Janknecht, PhD and Vassilios Sikavitsas, PhD	3D Model for Prostate Cancer Metastasis and the Role of KDM4 Histone Demethylases Therein
Dee Wu, PhD and Lei Ding, PhD	Functional Imaging Planning and Treatment of Necrotic Tumors
Carla Kurkjian, MD and Roger Harrison, PhD	New Enzyme Prodrug Therapy to Treat Colon, Pancreatic and Prostate Cancer

Evaluation Form

Evaluation Form
Stephenson Cancer Research Symposium
January 31, 2014

Instructions:

Your opinion of this activity is important to planning future events. Please indicate how you rate the event in the categories listed below by circling the number which indicates your response to each statement.

1 – Strongly Disagree 2 – Disagree 3 – Agree 4 – Strongly Agree

Physical Facilities

The physical facilities were adequate. 1 2 3 4
The environment was conducive to learning. 1 2 3 4

Oral Presentations

Keynote Speaker

The presentation was organized and easy to follow. 1 2 3 4
The speaker demonstrated knowledge / expertise in the area. 1 2 3 4
The content was based on current professional / scientific information. 1 2 3 4
The speaker clarified content in response to questions. 1 2 3 4
The presentation level was appropriate for the audience. 1 2 3 4

Session Presentations

The session presentations were organized and easy to follow. 1 2 3 4
The speakers demonstrated knowledge / expertise in the area. 1 2 3 4
The content was based on current professional / scientific information. 1 2 3 4
The presentations were at an appropriate level for the audience. 1 2 3 4

List the strengths of the Symposium.

List the weaknesses of the Symposium.

List any suggestions for future events.

