2013 Cancer Research Symposium

Symposium Keynote

Roy A. Jensen, MD

Director, The University of Kansas Cancer Center
Director, Kansas Masonic Cancer Research Institute
William R. Jewell Distinguished Kansas Masonic Professor

Cancer Health Disparities Keynote

Judith Salmon Kaur, MD

Professor of Oncology and Medical Director for
Native American Programs
Mayo Comprehensive Cancer Center

March 29, 2013 • Oklahoma City

Samis Family Education Center
University of Oklahoma Health Sciences Center

Co-sponsors:

OTRC OKLAHOMA TOBACCO
RESEARCH CENTER
Peggy and Charles
STEPHENSON CANCER CENTER
at The University of Oklahoma

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The Peggy and Charles Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Research Center (OTRC) for co-sponsoring the SCC 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: Laura Beebe, PhD

OTRC Co-Director: D. Robert McCaffree, MD

Program Coordinator: Laura DeLongy

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Cancer Research Symposium Schedule at a Glance

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                          Peggy and Charles Stephenson Cancer Center

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                          Roy A. Jensen, MD
                          Director, The University of Kansas Cancer Center
                          Director, Kansas Masonic Cancer Research Institute
                          William R. Jewell Distinguished Kansas Masonic Professor

9:15 - 9:30 a.m.   Break

9:30 - 10:30 a.m.   **Concurrent Sessions I**

10:30 - 10:50 a.m.   Break

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Cancer Research Symposium Concurrent Session Agenda

Basic/Translational/ Clinical Track (B/T/C)*
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*Basic / Translational / Clinical Track Moderator: Lawrence Rothblum, PhD

9:30 - 10:30 a.m.

B / T / C	**Tumor Cell Biology Session** Session Chair: Ralf Janknecht, PhD	Auditorium Level Two

LPA-Mediated Phosphorylation of P130CAS VIA Gαi2 And SRC Induces Invasive Migration of Ovarian Cancer Cells
Jeremy Ward

WNT Inhibitory Factor 1 Inhibits Human Salivary Gland Cancer Cell Growth: Novel Findings on Senescence and Cancer Stem Cells
Ilangovan Ramachandran, PhD

Fluvastatin Causes Downregulation of HCV Replication via a Cancer Stem Marker Doublecortin-like Kinase and Microtubule Bundling
Naushad Ali, PhD

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Understanding and Addressing Cancer Health Disparities in Indian Country
Judith Kaur, MD
Professor of Oncology and Medical Director for Native American Programs
Mayo Comprehensive Cancer Center

10:50 - 11:50 a.m.

B / T / C	**Tumor Microenvironment Session** Session Chair: Xin Zhang, PhD	Auditorium Level Two

Targeting Lung Tumor Angiogenesis: Translational Potential For LKB1 Tumor Suppressor Gene
Imoh Okon, PhD

RNA Binding Protein musashi-1 Regulates Tumorigenesis and Angiogenesis Via Microrna-Dependent Mechanism
Sripathi Sureban, PhD

The Cytokine Interleukin-22 (IL-22) Modulates Tumorigenesis in the Intestine
Lauren Zenewicz, PhD

CHD	**Building American Indian and Academic Partnerships in Cancer Health Research**	B3 Level B

Panel of Tribal and Academic Representatives
Facilitator: Dorothy Rhoades, MD

1:40 - 2:40 p.m.

B / T / C	**Therapy and Resistance Session** Session Chair: Doris Benbrook, PhD	Auditorium Level Two

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Lichao Zhao, MD, PhD

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4:10 - 5:10 p.m.

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- Cancer Functional Genomics Core
- Nuclear Magnetic Resonance Core
- Next Generation DNA Sequencing Core
- OUHSC Core Facilities

CHD   **Innovative Research to Enhance Tobacco Control**
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Lurdes Queimado, MD, PhD

Developing Serum Mass Profiling to Aid in Screening Patients with Small Pulmonary Nodules (SPNs)
Jay Hanas, PhD

Modified Risk Tobacco Products: Burden or Benefit to Individual and Public Health
Theodore Wagener, PhD

Keynote Speaker Biography

Roy A. Jensen, MD

Director, The University of Kansas Cancer Center Director, Kansas Masonic Cancer Research Institute
William R. Jewell Distinguished Kansas Masonic Professor
Professor of pathology and laboratory medicine, anatomy and cell biology, cancer biology, and molecular biosciences
The University of Kansas School of Medicine
The University of Kansas-Lawrence

Roy A. Jensen, MD was born in Kansas City, Kansas and earned his bachelor's degree in Biology and Chemistry from Pittsburg State University in 1980. He graduated from Vanderbilt University School of Medicine in 1984, and remained there to complete a residency in Anatomic Pathology and a Surgical Pathology fellowship under the direction of Dr. David L. Page. Following his clinical training he accepted a Biotechnology Training fellowship at the National Cancer Institute in the laboratory of Dr. Stuart Aaronson. He returned to Vanderbilt in 1991 and was appointed an Assistant Professor in the Departments of Pathology and Cell Biology. In 1993 Dr. Jensen was appointed as an investigator in the Vanderbilt-Ingram Cancer Center and assumed the management of the Human Tissue Acquisition and Pathology Shared Resource. Dr. Jensen was promoted to Associate Professor of Pathology and Cell Biology in 1996, and was appointed as an Associate Professor of Cancer Biology in 2001.

In 2004 Dr. Jensen returned home to Kansas and was appointed the William R. Jewell, M.D. Distinguished Kansas Masonic Professor, the Director of The University of Kansas Cancer Center, the Director of the Kansas Masonic Cancer Research Institute, Professor of Pathology and Laboratory Medicine, and Professor of Anatomy and Cell Biology at the University of Kansas Medical Center. He also holds appointments as a Professor in the Department of

Molecular Biosciences at the University of Kansas-Lawrence and as Professor in Cancer Biology at The University of Kansas Medical Center. Dr. Jensen is a member of several scientific and professional societies including the American Association for Cancer Research, the American Association for the Advancement of Science, the American Society for Cell Biology, the American Society for Investigative Pathology, and the United States and Canadian Academy of Pathology. He currently has over 150 scientific publications and has lectured widely on the clinical and molecular aspects of breast cancer pathology. Dr. Jensen's research interests are focused on understanding the function of BRCA1 and BRCA2 and their role in breast and ovarian neoplasia; and in the characterization of premalignant breast disease both at the morphologic and molecular levels. His laboratory was instrumental in demonstrating the role of BRCA1 in the growth control of normal and malignant cells and in how loss of functional BRCA1 contributes to the development of breast cancer.

Since becoming director of the cancer center in 2004, he has recruited a world-class leadership team and successfully led that team in achieving designation for The University of Kansas Cancer Center as a National Cancer Institute designated cancer center.

Concurrent Sessions:
Information
&
Abstracts

Concurrent Session 1 – Basic / Translational / Clinical

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

Tumor Cell Biology

Session Chair: Ralf Janknecht, PhD

9:30 a.m. – 9:50 a.m.	*LPA-Mediated Phosphorylation of P130CAS VIA Gai2 And SRC Induces Invasive Migration of Ovarian Cancer Cells* Jeremy D. Ward Ph.D. Candidate, Department of Cell Biology University of Oklahoma Health Sciences Center
9:50 a.m. – 10:10 a.m.	*WNT Inhibitory Factor 1 Inhibits Human Salivary Gland Cancer Cell Growth: Novel Findings on Senescence and Cancer Stem Cells* Ilangovan Ramachandran, PhD Department of Otorhinolaryngology University of Oklahoma Health Sciences Center
10:10 a.m. – 10:30 a.m.	*Fluvastatin Causes Downregulation of HCV Replication via a Cancer Stem Marker Doublecortin-like Kinase and Microtubule Bundling* Naushad Ali, PhD Department of Medicine, Section of Digestive Diseases Nutrition University of Oklahoma Health Sciences Center

LPA-MEDIATED PHOSPHORYLATION OF P130CAS VIA Gα_{i2} AND SRC INDUCES INVASIVE MIGRATION OF OVARIAN CANCER CELLS

Presenter: Jeremy Ward

[1,2]Jeremy D. Ward, [1,2]Danny N. Dhanasekaran
[1]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, [2]Department of Cell Biology, University of Oklahoma Health Sciences Center

Abstract: Ovarian cancer is the most deadly gynecological cancer, with previous studies implicating lysophosphatidic acid (LPA) in the progression of approximately 90% of all ovarian cancers. Nevertheless, the majority of the mechanisms through which LPA promotes ovarian cancer progression remain to be fully elucidated. Therefore, the underlying theme of our research is to identify novel LPA-activated signaling nodes that can be targeted for therapy in ovarian cancer. To this end, recent studies in our lab have identified p130Cas, a scaffold protein, is tyrosine phosphorylated in an LPA-dependent manner in ovarian cancer cells. p130Cas, upon tyrosine phosphorylation, recruits an array of signaling molecules that can promote tumor cell proliferation, survival, and metastasis and its overexpression has been linked to a significant decrease in overall survival in ovarian cancer patients, indicating the likely importance of LPA-mediated phosphorylation of p130Cas in ovarian cancer progression.

Oncogenic signaling by LPA involves the activation of at least six LPA-specific G protein-coupled receptors (LPARs). Currently, the majority of pathological effects of LPA-mediated signaling in ovarian cancer are thought to be mediated via the three Edg-family members. Relatedly, our present study identified LPAR1 (Edg-2) as the major facilitator of p130Cas phosphorylation in the ovarian cancer cells tested. Furthermore, previous studies have demonstrated that LPARs are coupled to the α-subunits of the heterotrimeric G protein families Gi, Gq, G12/13. Our current work identifies Gα_{i2} as the key G protein mediating tyrosine phosphorylation of p130Cas while revealing the G12-family inhibits tyrosine phosphorylation of p130Cas. Due to the involvement of both the Gi and G12 families in LPA-mediated migration, our study tentatively suggests a unique spatiotemporal coordination of signaling involving both the Gi and G12 families in order to facilitate invasive-migration of ovarian cancer cells. Moreover, our study demonstrates p130Cas phosphorylation is dependent on the tyrosine kinase, Src and can be potently inhibited with the FDA-approved Src inhibitor, Bosutinib. Furthermore, our current work indicates Src activation and subsequent p130Cas phosphorylation is the result of a direct activation of Src via Gα_{i2} and is Ras-independent.

Finally, using p130Cas-specific siRNA, we demonstrate p130Cas is a necessary downstream component of LPA-Gα_{i2}-induced migration and collagen-1 invasion of ovarian cancer cells. What is more, we demonstrate Gα_{i2}-p130Cas signaling, independent of exogenous LPA, can induce collagen-1 invasion and may utilize EMT to evoke this effect in ovarian cancer cells. Overall, our study is the first to establish the LPA-LPAR1- Gα_{i2} -mediated stimulation of p130Cas is involved in invasive migration of ovarian cancer cells.

WNT INHIBITORY FACTOR 1 INHIBITS HUMAN SALIVARY GLAND CANCER CELL GROWTH: NOVEL FINDINGS ON SENESCENCE AND CANCER STEM CELLS

Presenter: Ilangovan Ramachandran, PhD

[1]Ilangovan Ramachandran, [1]David Obeso, [2]Sripathi M. Sureban, [1]Antonio Reis1 and [1,3,4,5,6]Lurdes Queimado

Departments of [1]Otorhinolaryngology, [2]Medicine, [3]Cell Biology and [4]Pediatrics; [5]The Oklahoma Tobacco Research Center; [6]Peggy and Charles Stephenson Oklahoma Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

Background: The Wnt/β-catenin signaling pathway plays crucial roles in stem cell regulation and its aberrant activation contributes to the progression of several human cancers. We have demonstrated that Wnt inhibitory factor 1 (WIF1), a secreted Wnt antagonist, is down-regulated in salivary gland tumor cell lines. Here, we characterized the expression of WIF1 in human salivary gland tumor samples and unraveled the tumor suppressive mechanisms of action of WIF1 in salivary gland cancer cells.

Aims: 1) To characterize the WIF1 protein expression in a large series of human salivary gland tumors. 2) To determine the mechanisms leading to downregulation of WIF1 expression. 3) To study the anti-tumor effects of WIF1 in human salivary gland cancer cells.

Methods: WIF1 promoter methylation, loss of heterozygosity (LOH) and protein expression were determined in the human salivary gland normal and cancer samples by methylation-specific PCR, LOH and immunohistochemistry analyses, respectively. For in vitro studies, carcinoma ex-pleomorphic adenoma cells (CaExPA79) were transiently transfected with either empty vector or pCI blast-WIF1. Cell survival, cell cycle arrest and senescence were determined by MTT assay, flow cytometry and β-galactosidase staining, respectively. To determine the effects of WIF1 on cancer stem cells, we performed ALDEFLOUR assay by fluorescence-activated cell sorting (FACS) and spheroid formation assay.

Results: WIF1 was highly expressed in normal tissues, however, WIF1 expression was down-regulated in benign tumors and undetectable in over 80% of all malignant samples as studied by immunohistochemistry. LOH and methylation-specific PCR analyses demonstrated that both loss of genetic material and promoter hypermethylation contribute to WIF1 down-regulation in salivary gland cancer. WIF1 significantly inhibited the salivary gland cancer cell proliferation at all time points studied (24, 48 and 72 h). Cell cycle analysis showed a significant accumulation of cells in G1 phase suggesting that WIF1 induces G1 arrest in salivary gland cancer cells. Importantly, WIF1 caused a drastic increase in senescent cells while significantly reducing the self-renewal and the proliferation of cancer stem cells.

Conclusions: We demonstrate that WIF1 down-regulation by promoter hypermethylation and loss of genetic material is an important mechanism in human salivary gland cancer. WIF1 down-regulation occurs early in salivary gland oncogenesis and might predict a higher risk of progression to malignancy. Of major clinical importance, we show for the first time that WIF1 induces cellular senescence and significantly decreases cancer stem cell renewal and proliferation. Taken together, our study demonstrates the importance of WIF1 in the treatment of solid tumors, in particular, salivary gland cancer and delineates a novel tumor suppressive mechanism of WIF1.

Fluvastatin Causes Downregulation of HCV Replication via a Cancer Stem Cell Marker Doublecortin-like kinase and Microtubule Bundling

Presenter: Naushad Ali, PhD

[1,2]Naushad Ali, [1]Sripathi M. Sureban, [1]Randal May, [1]Heba Allam, [1,3]Ted Bader, [1]Michael S. Bronze, and [1,2,3]Courtney W. Houchen
[1]Department of Medicine, Section of Digestive Diseases and Nutrition, [2]Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK73104, [3]Department of Veterans Affairs Medical Center, Oklahoma City

Introduction: Chronic hepatitis C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC), the third most common cause of cancer-related deaths worldwide. We recently demonstrated that HCV induces overexpression of cancer stem cell (CSC) proteins including doublecortin-like kinase (DCLK1, formerly DCAMKL1). The DCLK1 expression level and number of DCLK1-positive cells are significantly increased in HCV patients with cirrhosis and dysplastic regenerative nodules. Downregulation of DCLK1 using specific siRNA results in inhibition of HCV replication. The cholesterol-lowering drug, fluvastatin (FLV) has been shown to possess antiviral and antitumor activities. Based on these observations, we hypothesized that FLV may interfere with DCLK1's role in HCV replication and HCC initiation.

Methods: Normal human hepatocytes (NHHs), HCV subgenomic replicon-expressing human hepatoma cells, and infectious HCV JFH1 were used to determine effects of varying amounts of FLV (0 through 10 uM) on HCV replication. Protein localization and expression in these cells were analyzed by confocal microscopy and Western blot. FLV cytotoxicity was determined by MTT and ATP assays. The target RNA levels were analyzed by real-time RT-PCR. The 3D spheroids assays of HCV-positive cells were carried out using Matrigel and magnetic lavitation methods.

Results: FLV induced bundling of microtubule filaments (MTFs) and also inhibited DCLK1 association with MTFs in HCV-expressing hepatoma cells. In contrast, NHH did not show detectable DCLK1 staining or FLV-induced MTF bundling. Unlike pravastatin (PRAV), FLV downregulated levels of HCV RNA, NS5A and NS5B polymerase. Two to three molar excess of FLV antagonist, mevalonic acid, failed to prevent FLV-induced inhibition of HCV and did not restore MTF dynamic instability. FLV diminished DCLK1 RNA levels in replicon model but did not affect miR-122, a key regulator of HCV expression and cholesterol biosynthesis. DCLK1 overexpression in hepatoma cells resulted in a 2-fold increase in the NS5B levels as compare to the control but did not prevent MTF bundling induced by FLV.

Conclusions: These studies unveiled a novel mechanism of FLV action that is, in part, independent of cholesterol synthesis pathway and but involves DCLK1 and MTFs. FLV is a useful adjunct for the treatment of HCV infection and prevention of HCC. The data strengthen the notion that FLV possesses antiviral and anti-tumor activities as it targets HCV as well as a CSC protein.

Concurrent Session 1 – Cancer Health Disparities

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

Keynote Address: Understanding and Addressing Cancer Health Disparities in Indian Country

Speaker: Judith Kaur, MD, Professor of Oncology and Medical Director for Native American Programs, Mayo Comprehensive Cancer Center

Dr. Kaur's address will review the significant health disparities in American Indian and Alaska Native communities, including cancer health disparities and inequities. She will highlight the prominent regional variations and present potential explanations. She will also describe community-based participatory research (CBPR), providing the example of the Mayo Comprehensive Cancer Center's Spirit of Eagles Community Networks Program, which serves as one proven approach for AIAN communities and academic medical centers to work together. Dr. Kaur urges that health planners and clinicians review aspects of the Indian Health Improvement Act to bring resources needed to overcome AIAN disparities.

Judith Salmon Kaur, MD

Professor of Oncology and Medical Director for Native American Programs, Mayo Comprehensive Cancer Center

Judith Salmon Kaur, MD, is the medical director for the Native American Programs of the Mayo Clinic Comprehensive Cancer Center. All three Mayo sites are involved in outreach to American Indians and Alaska Natives outreach s through the following programs:

- Native C.I.R.C.L.E. provides and develops culturally appropriate cancer education materials for lay persons, allied health and clinicians working in Native communities.
- "Spirit of Eagles" is a Community Networks Program with outreach nationally to American Indians and Alaska Natives, and it is the only national program working with AIAN populations.

Dr. Kaur's research also includes a special interest in women's cancers, particularly breast and cervical cancer. Dr. Kaur is a Professor of Oncology at Mayo Clinic College of Medicine. In addition, she is the Medical Director of the Mayo Clinic Hospice Program, as well as the Research Director for the Palliative Care Program and Course Director for an "Intensive Case-based Training in Palliative Care" for the Indian Health Service.

In 2007, Dr. Kaur was awarded "Physician of the Year" by the Association of American Indian Physicians. In the following year, 2008, she was appointed to the National Cancer Advisory Board by President George W. Bush and also became a Fellow of the American Academy of Hospice and Palliative Care. Dr. Kaur is Choctaw/Cherokee and is one of only two American Indian medical oncologists in the country.

Concurrent Session 2 - Basic / Translational / Clinical

10:50 a.m. – 11:50 a.m. Level Two, Auditorium

Tumor Microenvironment

Session Chair: Xin Zhang, PhD

10:50 a.m. – 11:10 a.m.
Targeting Lung Tumor Angiogenesis: Translational Potential For LKB1 Tumor Suppressor Gene
Imoh Okon, PhD
Department of Medicine, Molecular Medicine
University of Oklahoma Health Sciences Center

11:10 a.m. – 11:30 a.m.
RNA Binding Protein musashi-1 Regulates Tumorigenesis and Angiogenesis Via Microrna-Dependent Mechanism
Sripathi Sureban, PhD
Department of Medicine
University of Oklahoma Health Sciences Center

11:30 a.m. – 10:50 a.m.
The Cytokine Interleukin-22 (IL-22) Modulates Tumorigenesis in the Intestine
Lauren Zenewicz, PhD
Department of Microbiology and Immunology
University of Oklahoma Health Sciences Center

TARGETING LUNG TUMOR ANGIOGENESIS: TRANSLATIONAL POTENTIAL FOR LKB1 TUMOR SUPPRESSOR GENE

Presenter: Imoh Okon, PhD

[1]Imoh Okon, [1]Kathleen Coughlan, [1]Cate Moriasi, and [1,2]Ming-Hui Zou
[1]Section of Molecular Medicine, [2]Department of Biochemistry and Molecular Biology, College of Medicine, University of Oklahoma Health Sciences Center.

Introduction: Tumor angiogenesis and metastasis remain the leading causes of cancer-related mortality. Although anti-tumor properties of Liver Kinase B1 (LKB1) have been previously described in human neoplasm, a mechanistic link between LKB1 and tumor progression has yet to be fully explored. The prevalence of frequent LKB1 mutations in lung tumors (~30%) prompted investigation of its tumor suppressor functions in the disease. Here, we demonstrate the attenuation of tumor-promoting processes, including aberrant cell growth, angiogenesis and metastasis by LKB1 in vitro and in vivo.

Methods: Recombinant LKB1 protein or transient LKB1-vector was transfected into LKB1- deficient A549 lung cancer cells, while endogenous LKB1 expression was stably silenced in H1792, a stage IV, highly metastatic lung cancer cell line. Endogenous LKB1-expressing H1299 and H1703 lung cancer cell lines were also utilized. Angiogenesis was assessed by chorioallantoic membrane (CAM) assay which involved subcutaneous implantation of LKB1 null or positive cells into CAMs of 10-day old chick embryos, while tumor development and growth was investigated in nude mice. Cell proliferation and tumor metastasis, as a function of invasive and migratory potentials of LKB1-deficient or -expressing cancer cells was measured using the xCELLigence label-free, real-time system from Roche (Indianapolis, IN). Caspase-3 activity was determined by the EnzChek Caspase-3 Assay Kit #2 from Molecular Probes (Eugene, OR).

Results: LKB1-deficient A549 cells demonstrated strong angiogenic potential compared with LKB1-expressing H1299 or H1703 cell lines, as measured by vessel density in the CAM assay. Increased migration and invasion was also evident in A549 cells, indicative of a stronger metastatic potential compared with H1299 or H1703 cells. Ectopic gain-offunction experiments employing LKB1-expression vectors or recombinant LKB1 proteins correlated with decreased cell growth in A549 cells. Attenuation of AKT and caspase-3 signaling pathways contributed to the observed growth inhibition demonstrated by LKB1-expressing cells. Conversely, loss-of-function experiments utilizing stable LKB1 knock-down (shRNA) in H1792 cells correlated with tumor development and growth in nude mice, as well as increased angiogenesis in chick CAM assay. Enhanced migration and invasion was evident in LKB1-null cells compared with control (scramble shRNA) group.

Conclusion: LKB1-mediated repression of tumor growth, angiogenesis and metastasis was determined in vitro and in vivo. Recombinant LKB1 protein demonstrated strong anti-tumor growth properties suggesting potential development of an LKB1 mimetic for therapeutic applications. Furthermore, LKB1 or the loss of its expression could provide potential biomarker application in a subset of metastatic lung tumors.

In addition to the regulation of AMPK-mTOR pathway, and NF-κB transcription factor, novel mechanistic insights of anti-tumor LKB1 functions is currently under investigation.

RNA Binding Protein musashi-1 Regulates Tumorigenesis and Angiogenesis Via Microrna-Dependent Mechanism

Presenter: Sripathi Sureban, PhD

[1,2]Sripathi .M. Sureban, [1,2]Randal. May, [1]Dongfeng Qu, and [1,2]Courtney W. Houchen
[1]Department of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK;
[2]Veterans Affairs Medical Center, Oklahoma City, OK

Background and Aim: In the gut, tumorigenesis is thought to arise from the stem cell population located near the base of intestinal and colonic crypts. The RNA binding protein musashi-1 (Msi-1) is a putative intestinal stem/progenitor cell marker. We have previously published that Msi-1 expression is increased in human colorectal tumors and demonstrated its involvement in cancer cell proliferation, inhibition of apoptosis, and mitotic catastrophe. Epithelial-mesenchymal transition (EMT) plays a key role in cancer invasion/metastasis, and there is a gain of stem cell properties by the cells undergoing EMT. Tumor suppressor miRNAs like *let-7a*, *miR-144* and *miR-200* (*miR-200a, b* and *c*) are known to inhibit tumorigenesis and EMT. Recent studies suggest that *miR-200* targets transcription factors ZEB1 and ZEB2 leading to inhibition of EMT. Furthermore, *miR-200* also targets VEGF receptors (VEGFR) leading to inhibition of angiogenesis. Additionally, computational analysis of COX-2 3'UTR revealed a novel putative binding site for *miR-144*. We sought to determine whether Msi-1 regulates tumorigenesis and angiogenesis *via* miRNA-dependent mechanism.

Methods: HCT116, human colorectal adenocarcinoma cells were transfected with Msi-1 siRNA and tumor xenografts were treated with siRNA against Msi-1 and analyzed for Msi-1, c-Myc, Notch-1, CD31 (using immunoblot and/or real-time RT-PCR); ZEB1, ZEB2, Snail, Slug, Twist, COX-2, VEGFR1, VEGFR2 mRNA and microRNAs *pri-let-7a*, *pri-miR-144* and *pri-miR-200* (using real-time RT-PCR) levels. A luciferase reporter assay was performed using plasmids with binding sites (for *let-7a*, *miR-144*, *miR-200a* and *miR-200c*) at the 3' UTR to measure *let-7a*, *miR-144*, *miR-200a* and *miR-200c* in HCT116 cells.

Results: siMsi-1-mediated knockdown of Msi-1 resulted in HCT116 tumor growth arrest, with a downregulation of proto-oncogene c-Myc *via let-7a* miRNA dependent mechanism and a downregulation of Notch-1 *via miR-144* miRNA. Furthermore, knockdown of Msi-1 also induced *miR-200,* with subsequent down-regulation of EMT-associated transcription factors ZEB1, ZEB2, Snail, Slug and Twist. An increase in *let-7a*, *miR-144* and *miR-200* miRNAs was confirmed by a corresponding reduction in *let-7a*, *miR-144* and *miR-200* specific luciferase activity following the knockdown of Msi-1. Additionally, we also observed a significant down regulation of VEGF, VEGFR1 and 2 via *miR-200* and CD31 following the knockdown of Msi-1 demonstrating inhibition of angiogenesis. A significant downregulation of COX2 mRNA was also observed following the knockdown of Msi-1 probably via *miR-144.*

Conclusion: These findings illustrate an important direct regulatory links between Msi-1, miRNAs, EMT and angiogenesis in colorectal cancer. Msi-1 is a negative regulator of *let-*7a, *miR-144* and *miR-200* miRNA biogenesis. This may represent a novel target for anti-stem cell based therapies for colorectal cancer.

The Cytokine Interleukin-22 (IL-22) Modulates Tumorigenesis in the Intestine

Presenter: Lauren Zenewicz, PhD

Lauren A. Zenewicz, PhD
Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center

Introduction: Chronic mucosal inflammation and tissue damage predisposes patients to the development of colorectal cancer. This association could be explained by the hypothesis that the same factors and pathways important for wound healing also promote tumorigenesis. A sensor of tissue damage should induce these factors to promote tissue repair and regulate their action to prevent development of cancer. Interleukin-22 (IL-22), a cytokine of the IL-10 superfamily, has an important role in colonic epithelial cell repair, and its levels are increased in the blood and intestine of inflammatory bowel disease patients.

Methods: IL-22 deficient and control wild-type mice underwent the azoxymethane/dextran sodium sulfate (AOM/DSS) model of inflammation-mediated colon cancer. Wild-type mice may or may not have received neutralizing IL-22 antibodies during either the inflammatory or recovery phase. Inflammation during DSS-mediated colitis was examined by monitoring mass, colonoscopy and histology. Resulting tumor size and number was examined over time by colonoscopy and histology.

Results: IL-22, which is induced during intestinal tissue damage, exerted protective properties during the peak of damage, but promoted tumor development if uncontrolled during the recovery phase.

Conclusion: IL-22 critically regulates intestinal tissue repair and tumorigenesis in the colon.

Concurrent Session 2 – Cancer Health Disparities

10:50 a.m. – 11:50 a.m.   Level B, Room B3

Building American Indian and Academic Partnerships in Cancer Health Research

The goal for this session is to provide a forum for the exchange of experiences and ideas in collaborative partnerships between tribal entities and academic institutions engaging in cancer research within American Indian communities. Panelists are drawn from tribal health programs as well as academic institutions. After a brief review by Dr. Judith Kaur of the principles of community-based participatory research as a model, each panelist will be asked to share a particularly successful or unsuccessful experience in collaborative research and to provide a suggestion for enhancing future partnerships. Active audience participation will be sought to help identify themes that have hampered or helped cancer research among the American Indian population.

Moderator:

Dorothy Rhoades, MD, MPH, Director, American Indian Cancer Research Initiatives, Peggy and Charles Stephenson Cancer Center and Clinical Associate Professor of Medicine, Department of Internal Medicine, University of Oklahoma Health Sciences Center

Panelists:

Judith Kaur, MD, Professor of Oncology and Medical Director for Native American Programs, Mayo Clinic Comprehensive Cancer Center

Michael Peercy, MPH, Epidemiologist/Biostatistician, Chickasaw Nation Department of Epidemiology, Research and Public Health

Lisa Pivec, Director, Community Health Promotion and Healthy Nation Program, Cherokee Nation;

Everett R. Rhoades, MD, FACP, Professor Emeritus of Medicine and Senior Consultant for Center for American Indian Health Research, OUHSC

Lancer Stephens, PhD, Director, Special Populations Core, Peggy & Charles Stephenson Cancer Center

Dorothy Rhoades, MD, MPH

Department of Internal Medicine, University of Oklahoma Health Sciences Center, SCC

Research Interests: Dorothy Rhoades, MD, MPH, is the Director of American Indian Cancer Research Initiatives for the Peggy and Charles Stephenson Cancer Center and Clinical Associate Professor of Medicine in the Department of Internal Medicine.

Dr. Rhoades is a member of the Kiowa Tribe of Oklahoma. She earned her medical degree from the University of California, San Francisco School of Medicine and completed her internal medicine residency at the University of Colorado Health Sciences Center. She completed the American Indian Health Fellowship at the University of Washington where she also earned a Master of Public Health degree in epidemiology. She went on to complete the Native Investigator Development program at the University of Colorado Health Sciences for additional training American Indian health research. She then became faculty for the Native Investigator program, a role she continues today as mentor for American Indian junior investigators embarking on research careers in American Indian health. Her research focused on American Indian health with a particular focus on chronic diseases as well as quality of data available for the study of American Indian health disparities. Her current research focuses on American Indian cancer disparities.

She continued clinical work as a hospitalist for Group Health Permanente in Seattle, WA for nearly 15 years until September 2012 when she returned to Oklahoma to join the Department of Medicine as a hospitalist and the Stephenson Cancer Center faculty within the Cancer Health Disparities research section to develop research to address American Indian cancer health disparities.

Judith Salmon Kaur, MD

Native American Programs, Mayo Clinic Comprehensive Cancer Center

Research Interests: Judith Salmon Kaur, MD, is the medical director for the Native American Programs of the Mayo Clinic Comprehensive Cancer Center. All three Mayo sites are involved in American Indian and Alaska Natives outreach through the following programs:

•Native C.I.R.C.L.E. provides and develops culturally appropriate cancer education materials for lay persons, allied health and clinicians working in Native communities.

•"Spirit of Eagles" is a Community Networks Program with outreach nationally to American Indians and Alaska Natives, and is the only national program working with AIAN populations.

Dr. Kaur's research also includes a special interest in women's cancers, particularly breast and cervical cancer. Dr. Kaur is a Professor of Oncology at Mayo Clinic College of Medicine. In addition, she is the Medical Director of the Mayo Clinic Hospice Program, as well as the Research Director for the Palliative Care Program and Course Director for an "Intensive Case-based Training in Palliative Care" for the Indian Health Service.

In 2007, Dr. Kaur was awarded "Physician of the Year" by the Association of American Indian Physicians. In 2008, she was appointed to the National Cancer Advisory Board by President George W. Bush and also became a Fellow of the American Academy of Hospice and Palliative Care. Dr. Kaur is Choctaw/Cherokee and is one of only two American Indian medical oncologists in the country.

Michael Peercy, MPH

Department of Epidemiology, Research and Public Health, Chickasaw Nation

Research Interests: Michael Peercy is an Epidemiologist/Biostatistician with the Chickasaw Nation's Department of Epidemiology, Research and Public Health.   He completed an MPH from the University of Oklahoma in 2009. He is a certified Medical Technologist with a specialty in hematology and is a certified project management professional.   He is also a graduate of East Central University with an undergraduate degree in Psychology and Medical Technology. He has worked for the Chickasaw Nation Division of Health for 17 years in various positions including: Medical Technologist, Laboratory Information Systems Coordinator, Clinical Laboratory Manager, Health Information Technology Project Manager, and Epidemiologist.   He serves as the Chickasaw Nation Division of Health Institutional Review Board Administrator (IRB) and as an advisor to the Choctaw Nation IRB. He is a member of the Southern Plains Inter-Tribal Epidemiology Center advisory board, and is a National Member at Large for the American Indian/Alaska Native Health Research Advisory Council (HRAC) to the Department of Health and Human Services. Mr. Peercy is also the Native American Research Centers for Health (NARCH) liaison for the Chickasaw Nation. Mr. Peercy's program and research partnership interests include: bioethics, health disparities, environmental impacts on disease, geo-spatial analysis of disease, vector-borne illness, and cancer in Native American populations.

The Chickasaw Nation Division of Health works closely with academic and government partners on numerous research projects.   The Department of Epidemiology, Research and Public Health serves as a navigator and facilitator to increase the amount of quality research that takes place within the Chickasaw Nation. The primary goal of this new department is to encourage the development of community-based and community-driven research within the tribe.

Lisa Pivec, MS

Community Health Promotion, Cherokee Nation Health Services

Research Interests: Lisa Pivec, MS is the Director of Community Health Promotion for Cherokee Nation Health Services and has been with the Cherokee Nation since 1991. She directs the Healthy Nation Program, including the Male Seminary Recreation Center and serves as lead staff on the recently funded National Public Health Improvement Initiative from the Centers for Disease Prevention and Control. Ms. Pivec is the principal investigator for several funding agreements with the Centers for Disease Control and Prevention.

She recently served as the Accreditation Coordinator for Cherokee Nation's participation in the Public Health Accreditation Board Tribal Standards beta test, and she serves as the authorized representative from Indian Health Service Oklahoma Area for the Centers for Disease Control and Prevention Tribal Advisory Committee.

Ms. Pivec holds a master's degree from NSU in college teaching with an emphasis in health. She is citizen of the Cherokee Nation and is from the Peavine community in Adair County. She hopes to continue working with and for the Cherokee people throughout her career.

Everett R. Rhoades, MD, FACP

College of Medicine, University of Oklahoma Health Sciences Center

Research Interests: Everett R. Rhoades, MD, FACP, is Professor Emeritus of Medicine at the University of Oklahoma Health Sciences Center, and Senior Consultant to the University's Center for American Indian (AI) Health Research. During his distinguished career, he served as the first AI Director of the Indian Health Service with a rank of Rear Admiral and Assistant Surgeon General of the Public Health Service Commissioned Corps (1982-93). A member of the Kiowa Tribe of Oklahoma, Dr. Rhoades was instrumental in numerous local and national initiatives pertaining to AI and Alaska Native health including founding and serving on the Board of Directors for the Oklahoma City Indian Clinic in 1974, one of the largest urban Native American health centers. He served for 10 years on the Kiowa Business Committee and has also served as advisor for the Southwest Oklahoma Intertribal Health Board for many years. He is founding member of the Association of American Indian Physicians. He has numerous publications studying the health of Native Americans and continues to serve on the Steering Committee of the Strong Heart Study for which he chairs the Ethics Subcommittee and serves as tribal liaison. The Strong Heart Study is the largest longitudinal epidemiologic cohort study among AI. He is the editor of the peer reviewed book "American Indian Health -- Innovations in Health Care, Promotion and Policy" published by Johns Hopkins University Press in 2000. Among numerous honors he is the recent recipient of the 2012 American Medical Association Foundation Award for Excellence in Medicine.

Lancer Stephens, PhD

Department of Health Promotion Sciences, College of Public Health, University of Oklahoma Health Sciences Center
Special Populations Outreach Core, SCC

Research Interests: Lancer Stephens, PhD, an Assistant Professor of Research in the Department of Health Promotion Sciences, College of Public Health at the University of Oklahoma Health Sciences Center, and is the Director of the Special Populations Outreach Core for the Peggy and Charles Stephenson Cancer Center. He has been involved in developing research partnerships with Oklahoma's American Indian tribes since arriving at the University of Oklahoma Health Sciences Center in 2001. Currently, the Cancer Center Clinical Trials department has over 30% American Indian involvement. This involvement, as well as any research participation, is due to building trust and partnerships in meaningful research that provides tangible benefit.

He is an enrolled member of the Wichita tribe of Oklahoma through his father's side as well as half Muscogee (Creek) on his mother's side. He is of the tribal town Tvl-Mo.cv.se (translation; New Tulsa) and a member of the River Sand clan.

Concurrent Session 3 – Basic / Translational / Clinical

1:40 p.m. – 2:40 p.m.   Level Two, Auditorium

Therapy and Resistance

Session Chair: Doris Benbrook, PhD

1:40 p.m. – 2:00 p.m.

Accuracy-reducing Factors in Pap test for Patients with Invasive Cervical Cancer
Lichao Zhao, MD, PhD
Department of Pathology
University of Oklahoma Health Sciences Center

2:00 p.m. – 2:20 p.m.

Disseminated Sub-Lethal γ-Radiation Favors Autocrine/Paracrine Function and Endorses Radioprotection in Tumor Cells
Natarajan Aravindan, PhD
Department of Radiation Oncology
University of Oklahoma Health Sciences Center

2:20 p.m. – 2:40 p.m.

SHetA2 Decreases Mitoses and Growth, and Alters Pathology of MND-Induced Rat Mammary Tumors
Stan Lightfoot, MD
Department of Pathology
University of Oklahoma Health Sciences Center

Accuracy-reducing Factors in Pap test for Patients with Invasive Cervical Cancer

Presenter: Lichao Zhao, MD, PhD

Lichao Zhao, MD, Nicolas Wentzensen, MD, PhD, Roy R. Zhang, MD, S. Terence Dunn PhD, Michael A. Gold, MD, Sophia Wang, PhD, Mark Schiffman, MD, MPH, Joan Walker, MD, Rosemary Zuna, MD
Department of Pathology and Division of Gynecologic Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK and the National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: While cytologic screening for cervical cancer has been highly effective in decreasing the incidence of invasive cervical cancer, approximately 10,000 cancer cases are still diagnosed in the US each year. It is well known that tumor diathesis, blood and inflammation are present in the background of frankly malignant Pap tests that can potentially hamper specimen adequacy and accurate interpretation. This study was undertaken in an effort to document the diagnostic implications of these limiting factors in Pap Tests from women with cervical cancer.

Methods: 2937 women recruited into the SUCCEED study from 2002-2010 had ThinPrep Pap and HPV tests performed and interpreted in our laboratory. 276 of these women had a histologic diagnosis of invasive cervical cancer. In addition to adequacy, quality indicators were noted. HPV testing was performed on an aliquot of the cytologic sample using Linear Array (Roche) that uses PCR to detect 37 individual HPV genotypes. All findings were prospectively entered into a database for subsequent analysis.

The women were divided into Invasive Cancer (n=276) or No Cancer (Normal, CIN or AIS) based on the worst surgical pathology result. Cytologic and HPV results (positive/negative) were analyzed by cross sectional analysis using Pearson's chi square and Fishers Exact test.

Result: The unsatisfactory rate of cytology specimen from Invasive Cancer patients (2.9%, 8/276) was significantly higher than that in samples from the No Cancer group (0.9%, 23/2568) (p=0.008). The percentage ThinPrep slides with quality indicators noting the presence of obscuring blood or inflammation, or scanty cellularity was 37.7% (104/276) in specimens from Invasive Cancer patients compared with only 4.5% (116/2568) of the slides from the No Cancer group (p<0.0001).

In 5.4% (15/276) of patients with invasive cancer, the cervical cytology result was unsatisfactory, negative or ASC-US which suggests a delay to colposcopy and biopsy. Although absolute numbers for these cases were small, there was no difference in the HPV results for these cases (93.9%) versus those cancer cases with a diagnosis of LSIL or greater (91.6%) that would have referred the woman to colposcopy.

Conclusions: Higher rates of unsatisfactory and sub-optimal Pap tests from women with invasive cervical cancer challenge our ability to detect cervical cancer in women who have not participated in regular screening. It is important to recognize that such poor quality samples can harbor a malignancy and to design protocols to enhance detection in this setting. HPV tests can be abnormal even in samples unsatisfactory for cytology. Possible aids to diagnosis in this setting include 1) HPV co-testing in women over the age of 30; 2) reprocessing bloody, hypocellular samples to enhance cellularity; 3) rescreening unsatisfactory Pap tests in women with a poor screening history as "high risk".

Disseminated Sub-Lethal y-Radiation Favors Autocrine/Paracrine Function and Endorses Radioprotection in Tumor Cells

Presenter: Natarajan Aravindan, PhD

Natarajan Aravindan, PhD
Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Abstract: Induced radio-resistance in cancer cells surviving after radiotherapy could be associated with increased radioprotection limiting the therapeutic benefit of radiation. Herein we investigated the sequential mechanistic molecular orchestration involved in radiation induced radioprotection in tumor cells. Cells primed with LDIR (LDIR, 10, 50 or 100cGy) robustly and consistently increased CDIR-induced NFkB activity; decreased DNA fragmentation, apoptosis and cytotoxicity and; attenuates CDIR-inhibited clonal expansion. Further, NFkB manipulation studies with siRNA silencing or p50/p65 overexpression unveiled the influence of LDIR-activated NFkB in regulating CDIR-induced DNA fragmentation and apoptosis. LDIR significantly increased the transactivation/translation of radio-responsive TNFα, IL-1α, cMYC, SOD2. Co-culture experiments portraits LDIR-influenced radioprotection and increase in cellular expression/secretion/activation of radio-responsive molecules in bystander cells. Individual gene-silencing with siRNAs coupled with co-culture studies exhibits the influence of LDIR-modulated TNFα, IL-1α, cMYC and SOD2 in induced radioprotection in bystander cells. NFkB inhibition/overexpression studies coupled with co-culture experiments demonstrated that TNFα, IL-1α, cMYC and SOD2 are selectively regulated by LDIR-induced NFkB. Together, these data strongly suggests that scattered LDIR-induced NFkB-dependent TNFα, IL-1α, cMYC and SOD2 mediates radioprotection to the subsequent challenge dose in tumor cells.

SHetA2 Decreases Mitoses and Growth, and Alters Pathology of MND-Induced Rat Mammary Tumors

Presenter: Stan Lightfoot, MD

[1]Stan Lightfoot, MD, [2,4]Daniel Zhao, PhD, [3,4]Elangovan Thavathiru, PhD, [3,4]Doris M. Benbrook, PhD
[1]Departments of Pathology, [2]Biostatics, [3]OB/GYN, OUHSC

Background: SHetA2 (NSC721689) is a non-toxic chemoprevention drug that has completed pre-clinical testing by the NCI-RAID and RAPID programs and will be evaluated in a Phase 0 clinical trial under development. Previous studies found that SHetA2 reversed the cancerous phenotype and prevented carcinogenesis in organotypic cultures of human ovarian cancer and endometrial cells. The objective of this project was to evaluate the effects of oral SHetA2 on histologic features of tumors induced by the nitrosomethylurea (MNU) carcinogen in Sprague-Dawley rats.

Methods: SHetA2 was administered to 3 groups of 15 animals each in a Teklad diet formulated to contain 0 (control), 25 (low dose) and 50 (high dose) mg/kg/day. Five days later, each rat was injected with 11.25 mg of MNU into the peritoneum and the animals were continued on their respective diets. The first palpable tumors were noted 48 days after MNU injection. Tumors volumes were measured weekly. Four animals in the control group, one animal in the low dose group and one animal in the high dose group were euthanized early due to the excessive tumor size. Remaining animals were euthanized on day 85 and tumors were collected for histologic evaluation. H&E stained slides of the tumors were reviewed for histologic features in a blinded manner. A linear mixed model was used to compare the growth rate of tumor volumes. The fixed effects included treatment group and days. An unstructured covariance matrix was used in the model. The numbers of mitoses in the tumors of the different treatment groups were compared using a linear mixed model.

Results: Tumor growth rate was significantly lower in the high dose group in comparison to the control group (p=.004) and the low dose (p=.003). No significant difference (p=.716) in growth rate was observed between low dose and control groups. The number of mitoses counted in the tumors was significantly smaller in the high dose than in the control group (p=.004), but no significant difference was observed between low dose and control groups (p=.945). The histology of the tumors included fibrocystic disease, intraductal papillomatosis, adenoid cystic carcinoma, papillary carcinoma, papillary and adenoid cystic carcinoma and carcinoma. When compared per animal, there were no significant differences in the histologies between the treatment groups, however when each tumor was considered an individual data point, there was a statistical trend that both doses of SHetA2 decreased the percentage of papillary carcinoma and increased the percentages of adenoid cystic carcinoma, (high dose vs control: p=.058; low dose vs control: p=.058).

Conclusion: SHetA2 administered in the diet reduced cell proliferation, growth and aggressiveness of the pathologic diagnosis of mammary tumors in MNU-treated rats.

Concurrent Session 3 - Cancer Health Disparities

1:40 p.m. – 2:40 p.m.   Level B, Room B3

Translational Think Tank: Cancer Care to Primary Care

This session will engage attendees in a discussion of the challenges and opportunities associated with transitioning patients from oncology care to primary care after completion of acute phase cancer treatment. After an initial review of the published literature by Dr. Jim Mold, all session attendees are asked to contribute ideas about how to potentially make these transitions more effective 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 an effective oncology care-to-primary care system of patient care. At its conclusion, it is expected that a small working group with be formed to continue to drive progress in this area including application for funding to test proposed approaches.

Opening by:

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

Confirmed Think Tank Participants:

Robert Mannel, MD, Director, Stephenson Cancer Center

Joel Slaton, MD, Professor of Urology and Director, Urologic Oncology, Stephenson Cancer Center

George Selby, MD, Professor and Interim Section Chief, Hematology Oncology, Stephenson Cancer Center

Russell Postier, MD, Professor and Chair, Department of Surgery, OUHSC

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

Zsolt Nagykaldi, PhD, Associate Professor, OUHSC Department of Family and Preventive Medicine

Mike Pontious, MD, rural-based primary care

Kevin O'Brien, MD, community-based primary care

Brian Yeaman, MD, community-based primary care; health information exchange expert

Concurrent Session 4 – Basic / Translational / Clinical

2:50 p.m. – 3:50 p.m.   Level Two, Auditorium

Novel Methodologies

Session Chair: Rheal Towner, PhD

2:50 p.m. – 3:10 p.m.	*Laser Immunotherapy For Late-Stage, Metastatic Cancers* Wei Chen, PhD Center for Interdisciplinary Biomedical Education and Research Department of Engineering and Physics University of Central Oklahoma
3:10 p.m. – 3:30 p.m.	*A Potential New Method of Cancer Theranostics by Magneto-Thermo- Acoustics and Magnetically-Mediated Hyperthermia* Daqing Piao, PhD School of Electrical and Computer Engineering Oklahoma State University
3:30 p.m. – 3:50 p.m.	*Successful identification of novel glioma biomarkers using in-silico prediction of gene function* Jonathan Wren, PhD Oklahoma Medical Research Foundation

Laser Immunotherapy for Late-Stage, Metastatic Cancers

Presenter: Wei Chen, PhD

Wei R. Chen
Department of Engineering and Physics, College of Mathematics and Science, University of Central Oklahoma, Edmond, Oklahoma

Abstract: Laser immunotherapy (LIT) was developed with an ultimate goal in mind: eradicating metastatic cancers through a local intervention. LIT uses the combination of laser phototherapy and immunotherapy to target the immunological root cause of cancer. The laser photothermal interaction induces tumor deaths and tumor antigen release; application of glycated chitosan (GC), a novel immunological stimulant, induces tumor-specific immune responses. In our pre-clinical studies, LIT is shown to be highly effective against metastatic tumors in animals. We recently started clinical trials using LIT for the treatment of late-stage, metastatic melanoma and breast cancer patients. The experimental results indicate a systemic, long-term anti-tumor immunological response induced by LIT, using the entire tumor cell as the sources of tumor antigens, based on the principle of in situ autologous whole-cell cancer vaccination. LIT, if proven successful, could become an efficacious, cost-effective, minimally invasive, novel modality for patents with metastatic cancers who face severely limited options. In this presentation, the development, components, and procedures of LIT will be introduced. The progress of laser immunotherapy in clinical studies will be reported and the mechanism(s) of LIT will be discussed.

A Potential New Method of Cancer Theranostics by Magneto-Thermo- Acoustics and Magnetically-Mediated Hyperthermia

Presenter: Daqing Piao, PhD

[1]Daqing Piao, PhD, [2]Rheal A. Towner, PhD [3]Wei R. Chen, PhD
[1]School of Electrical and Computer Engineering, Oklahoma State Univerisity, Stillwater, OK, USA,
[2]Advanced Magnetic Resonance Imaging Center, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA, [3]Department of Engineering Physics, University of Central Oklahoma Edmond, OK, USA

Purpose: We propose a new mechanism to magnetically induce thermo-acoustic signal based on the heating of magnetic nanoparticles (MNPs) by an alternating magnetic field (AMF). As MNPs have the potential of molecularly specific conjugation with cancer markers, tracking and treating targeted magnetic nanoparticles for cancer theranostics may be feasible by using specifically patterned AMF for magneto-thermo-acoustic imaging and subsequent conventional AMF for magnetically mediated hyperthermia.

Methods: We present a theoretical analysis of the feasibility of thermo-acoustic wave generation from MNPs by applying a short burst of AMF or a frequency modulated AMF. As the relaxation of MNPs is strongly dependent upon the amplitude and frequency of AMF, either an amplitude modulated, fixed frequency AMF (termed time-domain AMF) or a frequency modulated, constant amplitude AMF (termed frequency-domain AMF) will result in time-varying heat dissipation from MNPs, which has the potential to generate thermo-acoustic waves. Following Rosensweig's model of specific power loss of MNPs in a steady-state AMF, the time resolved heat dissipations of MNPs of super-paramagnetic iron-oxide nanoparticles (SPIONs) when exposed to a short burst of AMF and/or to a linearly frequency chirped AMF are derived, and the resulted acoustic propagation is presented. Based on experimentally measured temperature rise characteristics of a SPION matrix in a steady-state AMF of various frequencies from 88.8 KHz to 1.105MHz, the heat dissipations of the SPIONs under time-domain and frequency-domain AMF configurations that could have practical utility for thermo-acoustic wave generation are estimated.

Results: The measured initial temperature rises of the SPION matrix of a 0.8mg/ml iron-weight concentration were characterized by Rosensweig's model, which predicted the heat dissipation at 10MHz AMF frequency to be 84 times of that at 1MHz. Exposing the SPION matrix to a 1 microsecond burst of AMF of 10MHz and 100 Oe field intensity will result in a volumetric heat dissipation of 7.7 $\mu J/cm^3$ over the micro second duration. This volumetric heat dissipation is comparable to the thermal energy dissipated upon a chromophore at several centimeters depth that is 100 times more absorptive than the background biological tissue of having a reduced scattering coefficient of 10cm-1 and an absorption coefficient of 0.1cm^{-1}. If the SPION matrix is exposed to a 1-ms long 100 Oe AMF train that chirps linearly from 1MHz to 10MHz, the volumetric heat dissipation over each 2π phase change of the AMF oscillation is estimated to increase from 0.15 to 1.1 $\mu J/cm^3$ within the millisecond duration.

Conclusions: Magneto-thermo-acoustic wave generation from MNPs by time- or frequency-domain AMF applications is feasible and, when combining with AMF-mediated hyperthermia, could render a potential new approach for targeted cancer theranostics.

Successful identification of novel glioma biomarkers using in-silico prediction of gene function

Presenter: Jonathan Wren, PhD

Jonathan D. Wren, PhD
Oklahoma Medical Research Foundation

Abstract: Despite the completion of the Human Genome almost 13 years ago, approximately a third of Human genes still have no known function. Furthermore, data from the ENCODE project has suggested that a majority of our genome is transcribed and the number of non-coding RNAs observed experimentally continue to grow. We hypothesized that within these uncharacterized transcripts are genes that could be used as biomarkers of cancerous processes, with the potential to aid in diagnostics, prognostics and therapeutics. We first constructed a transcriptional network using publicly available microarray and RNA-seq datasets to identify transcripts that tended to be co-expressed regardless of the experimental condition being studied. Then, to predict function, phenotype and disease relevance for transcripts that had yet to be characterized, we analyzed their significantly co-expressed transcripts in terms of what relationships had been reported in the peer-reviewed literature, scanning over 20 million MEDLINE records for transcript names and concepts that co-occurred with them. We experimentally tested 53 phenotypic predictions in a variety of in-vitro systems using RNAi, and 45 (85%) of the predicted phenotypes were validated. Within this set were 5 neural-expressed plasma-membrane-bound proteins that were uncharacterized or poorly characterized, predicted to be enriched in gliomas. Using MRI and an iron-labeled antibody to these proteins, we were able to visualize and validate that one of them, ELTD1, is present in the angiogenic region of rat gliomas. Using IHC, we validated that all 5 were enriched in malignant gliomas. Summary: Using in-silico predictions of transcript function enables the possibility of rapidly identifying novel markers and targets of cancerous processes. In combination with antibody-based technologies, this opens up possibilities for diagnosis, prognosis and therapeutics.

Concurrent Session 4 - Cancer Health Disparities

2:50 p.m. – 3:50 p.m.   Level B, Room B3

Cancer Health Disparities Research

This theme-related session will feature emerging research being conducted by Stephenson Cancer Center investigators on questions related to cancer prevention and control or cancer health disparities.

Session Chair:

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

Presenters:

Sydney Martinez, MPH, doctoral student, Department of Biostatistics and Epidemiology, College of Public Health, University of Oklahoma Health Sciences Center

Valarie Blue Bird Jernigan, DrPH, Assistant Professor of Health Promotion Sciences, College of Public Health, University of Oklahoma-Tulsa

Carol Rogers, RN, PhD, Assistant Professor, OUHSC College of Nursing, and Melissa Craft, RN, PhD, Assistant Professor, College of Nursing, University of Oklahoma Health Sciences Center

Zsolt Nagykaldi, PhD, Associate Professor, Department of Family & Preventive Medicine, College of Medicine, University of Oklahoma Health Sciences Center

CANCER INCIDENCE AND STAGING AMONG AMERICAN INDIANS IN OKLAHOMA, 2005-2009

Presenter: Sydney Martinez, MPH

[1]Janis E Campbell, PhD, [1]Amanda E. Janitz, RN MPH, [1]Sydney Martinez, MPH, PhD [2,3]Anne B Pate, PhD, [4]Julie Erb-Alvarez, MPH, [5]Cuyler Snider, MPH, [5]Tom Anderson, MPH
[1]Department of Biostatistics and Epidemiology, University of Oklahoma Health Sciences Center, [2]Oklahoma State Department of Health, [3]Chronic Disease Service, 4Oklahoma City Indian Health Service, [5]Oklahoma City Inter-Tribal Health Board

Introduction: Cancer is a serious cause of morbidity and mortality in the US and in Oklahoma. Disparities exist in incidence of cancer between American Indians and Alaska Natives (AI/ANs) and whites. The purpose of this study is to describe cancer among AI/ANs in Oklahoma.

Methods: Age-adjusted incidence rates obtained from OK2SHARE are presented for all cancer sites combined and for the most common cancer sites among AI/AN populations. These were compared to the rates of the white populations in Oklahoma from 2005 to 2009. Percentages of late stage cancers for breast, colorectal, and melanoma cancers are also presented.

Results: When accounting for misclassification, AI/ANs had a significantly higher overall cancer incidence rate than whites (629.8/100,000 vs. 503.3/100,000) with a rate ratio of 1.25 (95% CI: 1.22, 1.28). Females had an increased rate ratio between AI/ANs and whites at 1.31 (95% CI: 1.27, 1.35) compared to males at 1.19 (95% CI: 1.15, 1.23).

The percentage of late stage breast cancer from 2007 to 2009 was 31.0% for whites and 34.2% for AI/ANs, although the difference was not significant. For colorectal cancer, the percentage of late stage was also not significantly different between whites and AI/ANs, at 54.9% and 58.2%, respectively. There was a significant disparity in the percentage of late stage melanoma cancers between 2005 and 2009, with 14.0% late stage melanoma for whites and 20.0% for AI/ANs (p-value: 0.03).

Among 36 specific sites, 21 had rate ratios that were higher among AI/ANs compared to whites. Prostate cancer was the most commonly diagnosed cancer among both AI/ANs and whites. The rate ratio was significantly different at 1.10 (95% CI: 1.01, 1.16), with AI/ANs having a significantly higher incidence rate. Colorectal cancer also displayed a significantly higher rate among AI/ANs with a rate ratio of 1.50 (95% CI: 1.37, 1.58). Other primary sites demonstrating large disparities between the two populations included: kidney and renal pelvis (RR: 1.90, 95% CI: 1.70, 2.10), liver and bile duct (RR: 2.21, 95% CI: 1.84, 2.58), stomach (RR: 2.02, 95% CI: 1.63, 2.41) and gallbladder (RR: 3.40, 95% CI: 2.20, 4.60).

Discussion: Overall, we see disparities between AI/ANs and whites in Oklahoma similar to or greater than those seen in the US overall. Incidence rates were higher and stage at diagnosis was often worse for AI/ANs compared to whites. While the age-adjusted incidence rate was lower in females compared to males in both whites and AI/ANs, the rate was higher in AI/ANs compared to whites for both genders, with females having a higher rate ratio suggesting there is a larger racial disparity among females. AI/ANs had a significantly higher rate ratio for breast, colon and rectal, cervix uteri, kidney and renal pelvis, leukemia, lung and bronchus, non-Hodgkin lymphoma, prostate, and pancreatic cancer. AI/ANs had a significantly lower rate ratio than whites for bladder and melanomas of the skin.

IDENTIFYING "WINNABLE" POLICIES FOR OBESITY PREVENTION IN TRIBAL COMMUNITIES

Presenter: Valarie Blue Bird Jernigan, DrPH, MPH

[1]Valarie Blue Bird Jernigan , DrPH, MPH, [2]Leslie D. Carroll
[1]College of Public Health, Health Promotion Sciences Department, [2]College of Public Health, Masters of Public Health Program, University of Oklahoma-Tulsa

Introduction: Policy and environmental strategies to ensure access to healthy foods are increasingly recommended to address and prevent obesity. In 2009 the Centers for Disease Control and Prevention (CDC) recommended 24 evidence-based strategies and measures-- the Common Community Measures for Obesity Prevention (COCOMO)--to guide communities in identifying and implementing obesity prevention policy strategies. Of the 24 strategies, three specifically target increasing the availability of affordable healthy food and beverages and are relevant to rural settings. Such efforts are critical in Native American communities, where obesity rates double those of non-Hispanic Whites (43.2% versus 21.1%). Limited evidence suggests that rural and reservation Native communities lack access to food stores and to healthy foods within stores. However, researchers have never assessed the appropriateness of the COCOMO strategies in rural tribal communities. Neither have they adequately studied the readiness of tribal communities to implement such strategies.

Methods: This project assesses the feasibility of, and readiness to implement, the three COCOMO obesity prevention strategies focused on increasing healthy food availability within the Round Valley and Osage Indian Reservations in Northern California and Oklahoma. The tribal community advisory boards of each community have identified 100 community members and key stakeholders in each tribe (total n= 200) from diverse groups such as: tribal council members, community advisory members, school board officials, and tribal health authorities, among others. Community research partners in each community will administer a quantitative survey developed by Pitts et al to these stakeholders to assess the feasibility and likelihood of success of each of the three COCOMO strategies. To assess community readiness to act on obesity prevention, survey questions from the *Community Readiness Handbook* as adapted by Sliwa et al. to focus specifically on obesity prevention will also asked. These survey data will allow us to identify facilitators and barriers to enacting the most and least winnable policy options identified in the quantitative survey. Our specific aims are to: 1) rank selected COCOMO recommendations according to feasibility and likelihood of success given community culture, infrastructure, extent of leadership support, and likely funding support; and 2) assess community readiness to implement obesity prevention initiatives according to the *Community Readiness Model.*

Results: Data are currently being collected and findings will be shared.

Implications: Native Americans have critically high rates of obesity. A community's culture, infrastructure, extent of leadership support, and likely funding support are critical factors in assessing the most winnable obesity prevention strategies. A community's readiness to implement such strategies is also crucial to the success of any intervention. This study will advance this knowledge and thereby increase the likelihood for successful implementation of environmental obesity prevention and management strategies in tribal communities.

Sign Chi Do and Expressive Writing for Breast Cancer Survivors

Presenter: Carol Rogers, PhD, RN and Melissa Craft, PhD, RN

[1]Carol E. Rogers, PhD, RN, [1]Melissa Craft, PhD, RN
[1]College of Nursing, University of Oklahoma Health Sciences Center

Introduction: Early recognition and aggressive therapies are known to raise 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, has shown improved function, endurance, and physical activity among sedentary older adults. We hypothesize that SCD is enhanced by EW, and by specifically adapting two novel modalities, is more enjoyable, increases adherence to weekly practice, improves sleep, mood, and QOL, and reduces fatigue in breast cancer patients during treatment. Specific aims are: 1) In phase I, test the feasibility and acceptability of an adapted SCD/EW intervention on selected outcomes and anticipated burden of data collection among a group of breast cancer survivors who have completed treatment; 2) In phase II, with breast cancer patients in treatment, compare fatigue, sleep, mood, QOL, and PA outcomes between those in an adapted SCD/EW intervention with those receiving informational care. The purpose of this presentation is to discuss the design of this two phase study.

Theoretical Framework: The perceived stress experienced by breast cancer patients during treatment creates an ongoing process of assessing perceived threat, feelings of helplessness, and hypervigilance. This leads to an increased risk of functional decline due to sleep disruption and subsequent fatigue. We propose that participating in SCD/EW promotes adaptation to stressors of breast cancer therapy by increasing physical activity via the gentle movements and improving mood via the meditative effect of SCD combined with EW, thereby decreasing sleep disruption and fatigue.

Methods: This study will use a 2-Phase, mixed methods approach to adapt the SCD intervention and combine it with an EW activity: 1) Use participant feedback to adapt the original SCD/EW intervention, to meet therapeutic limitations, time constraints and accessibility needs of breast cancer patients in treatment; and 2) Evaluate acceptability and feasibility of intervention and measurement procedures by breast cancer patients in treatment for future studies; and 3) Test effects of the SCD/EW intervention compared to informational care on outcomes in breast cancer patients receiving treatment.

Implications: A specifically-adapted SCD, with meditation enhanced by EW, may improve sleep, mood, and QOL; reduce fatigue, and be both feasible and acceptable to women breast cancer survivors. If effective, this SCD/EW intervention will impact the long term QOL of breast cancer patients in a variety of urban and rural settings. Findings will provide preliminary work on the intervention for a future NCI grant application.

Novel Web-based Comprehensive Health Risk Appraisal May Improve Cancer Prevention in Primary Care Settings

Presenter: Zsolt Nagykaldi, PhD

[1]Zsolt J. Nagykaldi PhD, [2]Viola Voncken-Brewster MSc, [1]Cheryl B. Aspy PhD, [1]James W Mold MD, MPH
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Background: Health Risk Appraisals (HRAs) have been implemented in a variety of settings for prevention and health improvement, however few studies examined the impact of HRAs systematically in primary care.

Methods: Our team designed, implemented and pilot tested a novel, web-based, comprehensive and goal-directed HRA tool. We carefully pair matched and assigned four practices to control and intervention groups, yielding 200 participants. Patient and practice-level outcomes were measured before and 12 months after the implementation through the HRA questionnaire, patient surveys and qualitative feedback. Only intervention patients received feedback from the HRA, were encouraged to discuss the report at their next wellness visit and implement a personalized wellness plan.

Results: Bivariate analyses suggested that estimated life expectancy (ELE) and its derivatives, including Real Age and Wellness Score were significantly impacted by the HRA implementation. The overall rate of preventive maneuvers that included 10 services improved by 4.2% in the intervention group (P=0.001 vs. control). A difference-in-differences analysis demonstrated that the HRA improved the patient-centeredness of care, measured by the CAHPS PCC-10 survey (0.74 point increase on a 10-point scale; P=0.05). Logistic regression models, adjusting for age, gender and the number of comorbidities indicated that HRA use was strongly associated with better self-rated overall health (OR: 4.94; P<0.0001), in addition to improved uptodateness for preventive services (OR: 1.22; P=0.02). A generalized linear model that controlled for age and gender suggested that increase in Wellness Score was associated with improvements in patient-centeredness of care, uptodateness for preventive services and being in the intervention group, while it showed an inverse relationship to the number of visits, comorbidities, BMI, and smoking (all P<0.03).

Conclusions: Despite study limitations, results strongly suggest that a comprehensive, web-based, and goal-directed HRA tool can improve the receipt of preventive services, patient-centeredness of care, behavioral health outcomes, and various wellness indicators in primary care settings.

Concurrent Session 5 - Basic / Translational / Clinical

4:10 p.m. – 5:10 p.m.   Level Two, Auditorium

Stephenson Cancer Center Shared Resources

4:10 p.m. – 4:20 p.m.   Molecular Imaging Core

4:20 p.m. – 4:30 p.m.   Cancer Tissue Pathology Core

4:30 p.m. – 4:40 p.m.   Cancer Functional Genomics Core

4:40 p.m. – 4:50 p.m.   OMRF Nuclear Magnetic Resonance Core

4:50 p.m. – 5:00 p.m.   OMRF Next Generation DNA Sequencing Core

5:00 p.m. – 5:10 p.m.   OUHSC Core Facilities

Concurrent Session 5 - Cancer Health Disparities

4:10 p.m. – 5:10 p.m.   Level B, Room B3

Innovative Research to Enhance Tobacco Control

This session will feature three selected, Oklahoma Tobacco Research Center (OTRC)-funded research projects demonstrating the transdisciplinary and cross-cutting research investment made by OTRC.

Session Chair:

Laura Beebe, PhD, Professor of Epidemiology, OUHSC College of Public Health, and Director, Oklahoma Tobacco Research Center

Presenters:

Lurdes Queimado, MD, PhD, Associate Professor, Departments of Otorhinolaryngology, Cell Biology and Pediatric Medicine, College of Medicine, University of Oklahoma Health Sciences Center

Jay Hanas, PhD, Professor of Biochemistry and Molecular Biology, College of Medicine, University of Oklahoma Health Sciences Center

Theodore Wagener, PhD, Assistant Professor in General and Community Pediatrics, Department of Pediatric Medicine, College of Medicine, University of Oklahoma Health Sciences Center

Assessing In Vivo DNA Damage to Predict Susceptibility to Tobacco-Induced Disease in Diverse Populations

Presenter: Lurdes Queimado, MD, PhD

[1]Vengatesh Ganapathy, [1]Wilbur Mills, [1]Ilangovan Ramachandran, [1]Elangovan Thavathiru, [2]Leslie Chandler, [1]Dini Chissoe, [5]Lancer Stephens, [1-5]Lurdes Queimado
[1]Departments of Otorhinolaryngology, [3]Cell Biology and [4]Pediatrics; [2]The Oklahoma Tobacco Research Center, and [5]The Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center

Background: Tobacco misuse is the leading preventable cause of morbidity and mortality in the world. Tobacco-induced DNA damage is one of the main mechanisms contributing to the pathogenesis of cancer, stroke, heart and pulmonary diseases. Tobacco-induced DNA damage is modulated by genetic and epigenetic factors, as well as life-style choices, and is expected to be a major determinant of the individual susceptibility to tobacco-induced diseases. 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.

Recently, we developed a novel primer-anchored DNA damage detection assay (PADDA) that reliably maps and quantifies endogenous and induced DNA damage. PADDA is the only available assay able to detect DNA damage caused by endogenous agents, and has higher sensitivity than other available assays to detect DNA damage caused by exogenous agents.

Aims: (1) To standardize PADDA for the detection of oxidative DNA damage, one of the main types of both endogenous and tobacco-induced damage; (2) To define the levels of persistent DNA damage in the oral mucosa of smokers in diverse populations. (3) To determine if the levels of tobacco-induced DNA damage vary significantly between ethnic groups.

Methods: To standardize the assay, PADDA was used on a high-throughput setting to quantify DNA damage in oral cell lines exposed to very low doses of hydrogen peroxide. DNA damage was mapped and quantified on the p53 gene by PADDA in oral epithelial cells collected from smokers and non-smokers by oral scrapings in two distinct populations: Caucasians and American Indians. Saliva cotinine levels were determined and used to confirm smoking status. Data were analyzed by chi-square goodness of fit and exact non-parametric tests.

Results: Our data documented PADDA's ability to detect dose-dependent increase in oxidative DNA damage in human oral cells. DNA damage was significantly higher in smokers than in non-smokers. Remarkably, we observed for the first time a significant difference in levels of tobacco-induced DNA damage between DNA strands. Studies are on-going to determine if the levels of tobacco-induced DNA damage vary significantly between ethnic groups.

Conclusion: PADDA detects dose-dependent DNA damage response, a crucial test of its 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, for the first time, that tobacco-induced DNA damage accumulates preferentially in one DNA strand. 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.

Developing Serum Mass Profiling to Aid in Screening Patients with Small Pulmonary Nodules (SPNs)

Presenter: Jay Hanas, PhD

[1]Jay S. Hanas PhD, [1]James R. Hocker, MS, [2]Megan R. Lerner, [3]Stan A. Lightfoot, MD, [4]Daniel J. Bracket, [2]Donald E. Stowell, MD, [2]Marvin D. Peyton, MD
[1]Department of Biochemistry, [2]Department of Surgery, [3]Department of Pathology, University of Oklahoma Health Sciences Center, [4]VA Medical Center, Oklahoma City, Oklahoma

Background: Lung cancers are the leading cause of cancer deaths in the United States and also world-wide. These cancers have a low 5 year survival rate (15%), as they are rarely diagnosed in an early-stage where cures are more attainable with surgery. The technology of low-dose computed tomography (CT) has been shown to possibly reduce the lung cancer mortality rate by its ability to screen/identify potentially malignant small/solitary pulmonary nodules (SPNs).

Distinguishing malignant versus non-malignant categories of SPNs in patients, e.g., like those identified on CT scans, is therefore an important albeit problematic and costly process in lung cancer screening. The majority of high-risk cigarette smokers have such nodules, and it is important to develop low-cost and non-invasive technology to assist in this screening process. Our research group is having success distinguishing sera of early-stage non-small cell lung cancer (NSCLC) patients from healthy control individuals using a novel approach involving electrospray ionization (ESI) mass spectrometry (MS) and quantitative/statistical mass peak analyses. In this report we provide evidence for the potential of our mass profiling technology for distinguishing patients with non-malignant versus malignant SPNs.

Modified Risk Tobacco Products: Burden or Benefit to Individual and Public Health

Presenter: Theodore Wagener, PhD

[1,2]Theodore L. Wagener, PhD, [2]Leslie Quinalty, MS, [2]Maggie Warner, BS, [4]Ellen Meier, MS, [3]Elisha Oliver, MS, [2]Danielle M. Wierenga, [4]Alayna Tacket, BA
[1]Oklahoma Tobacco Research Center, [2]Oklahoma University Health Sciences Center, [3]University of Oklahoma-Norman, [4]Oklahoma State University, [5]Brown Medical School, [6]Medical University of South Carolina, [7]University of Minnesota, [8]Boston University School of Public Health

Background: Tobacco smoking is by far the leading cause of preventable death in the U.S. and the world, killing an estimated 5 million people a year. Some argue, and the evidence is beginning to suggest, that approximately 90% of the harm from tobacco smoking is a result of the tobacco being burned, and much less due to the other constituents of the tobacco product. Therefore, with increased pressure due to smoking bans, the populations awareness of the poor health effects of smoking, and a declining revenue stream, the tobacco industry has begun to develop, manufacture, and sell "cleaner" delivery mechanisms of nicotine—modified risk tobacco products (MRTPs). MRTPs such as low-nitrosamine tobacco (e.g., Ariva/Stonewall, Camel Orbs, Snus) and electronic cigarettes all deliver nicotine to the user and do so without the harmful effects of combustion, producing no smoke or carbon monoxide. However, many of these products continue to expose the user to carcinogenic tobacco specific nitrosamines and polycyclic aromatic hydrocarbons, making them relatively less harmful than cigarettes but not harmless overall. With the development of these new products, the tobacco control community has become divided, with some seeing these products as a potential burden to public health and others seeing them as a potential benefit. Many questions need to be answered before we will fully understand the implications of MRTP use by current and future smokers and the overall population effects. Our lab has attempted to begin to address some of these questions by examining the following: 1) the chemical constituents of secondhand vapor and "e-liquid" from electronic cigarettes and its cytotoxicity; 2) the use of electronic cigarettes on smoking behavior, smoking beliefs, motivation to quit smoking, and pulmonary functioning; 3) the use of dissolvable tobacco products and electronic cigarettes on parents smoking behavior/beliefs and on their children's level of secondhand smoke exposure and pulmonary functioning; and 4) the perception and use of MRTPS versus other tobacco products by college students. Overall, our preliminary results suggest that the MRTPs that we have investigated are potentially safer than regular cigarettes, increase motivation and confidence to quit smoking, reduce the number of cigarettes smoked, and reduce the level of secondhand smoke to which children living with smokers are exposed.

Poster Presentation Abstracts

Cancer Research Symposium Poster Session

11:50 p.m. – 1:40 p.m.   Level 1

Poster Presentation List (listed A-Z by presenter)	Poster Location	Track
Evaluation of Effect of OKC-007 on Tumor Heterogeneity In Gliomas Using Diffusion Weighted Imaging Balasubramanian, Krithika	43	B/T/C
HuR as a molecular target for radio sensitization of human breast cancer cells Basalingappa, Kanthesh	44	B/T/C
Novel Small Molecules with Anticancer Activity in Triple Negative Breast Cancer Bastian, Anja	29	B/T/C
The JMJD2B Histone Demethylase: Tumor Promoter and Drug Target Berry, William	30	B/T/C
Far-Red Light-activatable Prodrug of Combretastain A-4 Using Photo-Unclick Chemistry: Synthesis, In Vitro and In Vivo Studies Bio, Moses	45	B/T/C
Cancer Functional Genomics Core	28	Shared Resource
Mesenchymal Stem Cells Combining Hollow Silica Nanoparticles as Target Vector Toward Breast Tumor Photodynamic Therapy Cao, Binrui	46	B/T/C
Implementation of a Community-Based Participatory Research Training to Address Obesity Carroll, Leslie	58	CHD
Role of DCLK1+Stem Cells in Epithelial- Mesenchymal Transition and Intestinal Neoplasia Chandrakesan, Parthasarathy	47	B/T/C
Reduced Expression of Aldo-Keto Reductase Family Member C3 (AKR1C3) in Neuroendocrine Cells and Neuroendocrine Tumors in the Areodigestive Tract Chang, Theodore S.	48	B/T/C
Effects of OKN-007 IN A F98 Glioma Model Assessed by 1H MR Spectroscopy Coutinho de Souza, Patricia	31	B/T/C
Molecular MRI Differentiation of VEGFR2 Levels in Four Different Experimental Anti-Glioma Therapies within a GL261 Mouse Model Coutinho de Souza, Patricia	32	B/T/C

Cohesion Fatigue: Chromatid Separation in the Absence of Cohesion Cleavage Daum, John	1	B/T/C
Perceived Barriers to HPV Vaccination by American Indian Teens and Caregivers Eschiti, Valerie	64	CHD
Cancer-Related Education and Goal Attainment in Comanche Nation Finch, Toni	57	CHD
Examining the Chemical Constituents of Secondhand Vapor Foster, Steven B.	66	CHD
EWI-2/PGRL Inhibite Cancer Cell Motility Via Down Regulation of Epithelial- Mesenchymal Transition Fu, Chenying	2	B/T/C
Padda, A Novel Assay to Characterize Mainstream And Side stream Smoke Induced DNA Damage Ganapathy, Vengatesh	63	CHD
The gep protooncogene Ga12 Mediate LPA-Stimulated Activation of CREB in Ovarian Cancer Cells Ha, Ji Hee	3	B/T/C
Targeting Single-Walled Carbon Nanotubes for the Treatment of Breast Cancer using Photothermal Therapy Harrison, Roger	4	B/T/C
Nucleoside Transporter Function In Cancer Therapy Hays, Franklin A.	5	B/T/C
Eliminating Tobacco-Related Cancer Health Disparities In Oklahoma Workplaces: A Qualitative Policy Evaluation Helt, Angela; Davis, Arian	59	CHD
How CD82 Inhibits Cancer Cell Migration from Cholesterol Binding Motif to Membrane Thermodynamics Huang, Chao	33	B/T/C
Categorization of CIN Categorization Lesions According to Immunohistochemistry and HPV Genotype Husain, Sanam	6	B/T/C
Formulation and characterization of SHetA2 capsules for phase 0 clinical trials Ibrahim, Mariam	42	B/T/C
Molecular Imaging Core	26	Shared Resource
Role of Gonadotrophines on Intestinal Tumorigenesis Janakiram, Naveena B.	7	B/T/C

Patterns of Care for Localized Breast Cancer in Oklahoma 2003-2006 Janitz, Amanda E.	60	CHD
Congenital Anomalies and Childhood Cancer in Oklahoma: A Linkage Analysis Janitz, Amanda E.	61	CHD
Radiation Induced TNFa Dependent Second Signaling Feedback Associated Post-Translational Nuclear-Import of NFkB Regulates Tumor Invasion/ Metastasis in Human Neuroblastoma Khan, Faizan H.	8	B/T/C
Potential of Turmeric Fractions in Mitigating the Onset of Oncogenesis in Mouse Model of Radio- Protection Khan, Faizan H.	9	B/T/C
Impact of Histone Demethylase JMJD2A on Prostate Cancer Development Kim, Tae-Dong	49	B/T/C
Development and Evaluation of a Vascular-Targeted Enzyme Prodrug Therapy For Breast Cancer Krais, John	34	B/T/C
Structure Activity Relationship Studies to Improve Cancer Drugs Kriewall, Caitlin; Carroway, Wm. Preston; Magiera, Kelsie	35	B/T/C
Differential Roles of Autophagy in Ovarian Cancer and Healthy Cells in Response to ShetA2 Drug Long, Andrew	36	B/T/C
Health Beneficial Effects of Dietary Omega-3 Polyunsaturated Fatty Acids (n-3) on the Obesity-Associated Disease and Cancers Studied by Nutritional Proteomics Matsumoto, Hiroyuki	10	B/T/C
Contribution of EMT Radiation resistance of Breast Cancer Mehta, Meghna	11	B/T/C
Structural Studies of Human JMJD4 with X-Ray Methods Mooers, Blaine	12	B/T/C
Pelitinib Regulates Radiation-Induced p65- Dependent Telomerase Activation In Head and Neck Squamous Cell Carcinoma Natt, Praveen	13	B/T/C
Irreversible EGFR Tyrosine Kinase Inhibitor, EKB-569 Potentiates Radiotherapy In Tumor Cell Killing Natt, Praveen	14	B/T/C
Targeting Lung Tumor Angiogenesis: Translational Potential For LKB1 Tumor Suppressor Gene Okon, Imoh	50	B/T/C

Qualitative Interviews with Smokers Following E-Cigarette Sampling Oliver, Elisha R.	62	CHD
Radiation-Induced MMP9 Maintains REL Signaling Through Second-Signaling Feedback Via Both ERK and IKK Activation and Endorses Delayed Invasion and Metastasis of Neuroblastoma Pandian, Vijayabaskar	51	B/T/C
Anti-Oxidant Rich Seaweed Polyphenols Target Multi-Signaling Cascase and Alleviats Pancreative Cancer Progression Pandian, Vijayabaskar	52	B/T/C
IL-24 Phosphorylation is critical in regulating the AKT-mTOR Signaling Pathway Associated with Cancer Survival and Metastasis Panneerselvam, Janani	53	B/T/C
Targeted Enzyme ProDrug Therapy for Metastatic Prostate Cancer - A Comparative Study of Three Fusion Proteins Passlack, Katrin	37	B/T/C
Descriptive Epidemiology of Malignant Melanoma in Oklahoma 2000-2012 Pate, Anne	67	CHD
Seed Mediated Synthesis of Dendritic Gold Nanoparticles with Efficient Photothermal Cancer Cell Killing and Catalytic Prospects Qiu, Penghe	54	B/T/C
Tumor-homing nanoparticles for targeted breast cancer imaging and treatment Qu, Xuewei	38	B/T/C
High Sensitivity DNA Damage Detection Assay: Potential Took to Predict Cancer Risk and Response to Treatment Queimado, Lurdes	15	B/T/C
Activatable Photosensitizers for Mitochondrial Targeting and Photodynamic Therapy Rajaputra, Pallavi	39	B/T/C
Diet Derived Polyphenol Targets EMT and Pluripotency Maintenance Transcriptome In Pancreatic Cancer Stem Cells Ramraj, Satish K.	16	B/T/C
Anti-metastatic Potential of Sulfated Polysaccharides from Turbinara conoides in Pancreatic Cancer Ramraj, Satish K.	17	B/T/C
Selective Targeting and Treatment of Pancreatic Cancer Via Three Fusion Protein/Prodrug Complexes plus Docetaxel Restuccia, Antonietta	18	B/T/C

Role of TICRR in DNA Replication Sansam, Courtney G.	19	B/T/C
AMPkaI Deficiency Increases DNA Damage and Genomic Instability Song, Ping	20	B/T/C
Roles of Heat Shock Protein 9 and BCL-2 in the Mechanism of ShetA2 Inhibition of Rat Mammary Tumors Thavathiru, Elangovan	21	B/T/C
Tissue Pathology Core	27	Shared Resource
Promoting Regular Screening Mammography In An American Indian Community in Oklahoma Tolma, Eleni	68	CHD
Combined Molecular MRI and Immuno-Spin-Trapping for In Vivo Detection of Membrane- Bound Radicals in Mouse GL261 Gliomas Towner, Rheal	22	B/T/C
Primary CNS Ewing Sarcoma: A Report of 2 Cases VandenHeuvel, Katherine A.	55	B/T/C
Development of a General Framework for Effective Translation of In Vitro Synergistic Combination into In Vivo Synergy Using a Systemic Modeling Approach Vega-Villa, Karina R.	56	B/T/C
The Effect of E-Cigarette Sampling on Smoking Behavior and Motivation and Confidence to Quit Smoking Wagener, Theodore L.	69	CHD
E-Cigarettes: Their Effects on Smoking Behavior, Pulmonary Functioning, and Motivation and Confidence to Quit Smoking Wagener, Theodore	70	CHD
Docosahexaenoic Acid (DHA) Increases Heme Oxygenase - 1 (HO-1) Expression by Enhancing BTB and CNC Homology 1 (BACH1) Degradation in Human Cancer Cells Wang, Shuai	40	B/T/C
LPA-Mediated Phosphorylation of P130CAS VIA Gai2 And SRC Induces Invasive Migration of Ovarian Cancer Cells Ward, Jeremy	41	B/T/C
Obesity Prevalence among Low-Income Children in Oklahoma WIC 2005-2010 Weedn, Ashley	65	CHD
Modeling Pediatric Cancers in Zebrafish West, Kyle	23	B/T/C

Zinc At Non-Cytotoxic Concentrations Up-Regulates Heme Oxygenase-1 (HO-1) Expression through the NRF-2 Signaling Pathway in Human Cancer Cells
Xue, Jing   24   B/T/C

Up-Regulation of Organic Anion Transporting Polypeptide (OATP) 1B3 Transport Activity by Proteasome Inhibition
Yue, Wei   25   B/T/C

EVALUATION OF EFFECT OF OKN-007 ON TUMOR HETEROGENEITY IN GLIOMAS USING DIFFUSION WEIGHTED IMAGING

Presenter: Krithika Balasubramanian, PhD

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Introduction: Glioblastoma Multiforme is a malignant WHO grade IV glioma with a poor prognosis in humans. In this study, we assess the response of heterogenous tumor regions following treatment with the anti-cancer agent, OKN-007, in rat F98 glioma models using diffusion weighted magnetic resonance imaging (DW-MRI).

Two groups of rat F98 gliomas (treated with OKN-007 and untreated) were monitored using DW-MRI (parameters: repetition time (TR)/ echo time (TE) = 3750/ 51.1 ms, matrix size = 128x128, no. of b values = 5, b values = 200-3000 s/mm2). Tumor volume was measured on the T2-weighted images (TR/ TE = 5000/ 50 ms, matrix size = 256x256, average = 4).   For calculation of apparent diffusion coefficient (ADC), uniform circular regions of interest (ROIs) were drawn on the ADC map in the various regions of the tumor as well as the normal contralateral regions.

Different regions of the tumor could be distinguished from each other based on the ADC values. Between the untreated and the treated group, significant decrease was observed in the ADC of the tumor core in the treated group compared to that of the untreated group. The ADC of the necrotic region in the treated group also showed decrease, although not significant, compared to the untreated group. The study indicates that OKN-007 mediates varying effects on different regions of the tumor. Diffusion MR enables clear distinction of tumor heterogeneity and aid in the assessment of therapeutic response.

HuR as a molecular target for radio sensitization of human breast cancer cells

Presenter: Kanthesh Basalingappa, PhD

[1]Kanthesh M Basalingappa, [1]Meghna Mehta, [2,3]Rajagopal Ramesh and [1,3]Anupama Munshi
Departments of [1]Radiation Oncology, [2]Pathology and [3]Peggy and Charles Stephenson Oklahoma Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA

Abstract: Hu antigen R (HuR) or embryonic lethal abnormal vision 1 (ELAVL1) is the ubiquitous member of the ELAV/Hu family of RNA-binding proteins. HuR is involved in the control of cellular differentiation and apoptosis and is associated with carcinogenesis through the regulation of angiogenesis and lymphangiogenesis. HuR is predominantly localized in the nuclei of most unstimulated cells, but upon cell stimulation translocates to the cytoplasm where it stabilizes target mRNA's. Increased cytoplasmic HuR expression has been detected in human cancers and is often associated with the aggressiveness of the cancers, including those of the breast. Stress-activated signaling pathways have been shown to modulate the cytoplasmic abundance of HuR and its RNA-binding function. Emerging experimental data suggests that cytoplasmic localization of HuR and its interaction with the MAPK pathway leads to tamoxifen resistance. Although a potential role of HuR in mediating resistance to tamoxifen has been shown, its role in mediating resistance to radiation therapy has not been investigated. In the present study, we tested the hypothesis that cytoplasmic accumulation of HuR may dictate radiation response of breast cancers. To test this hypothesis we examined HuR expression levels and its subcellular distribution in a panel of breast tumor and normal cell lines. Cytoplasmic and nuclear extracts were isolated from the cell lines following exposure to radiation (5 Gy) and assessed for HuR at different time points (0.5, 1, 2 and 24 h). Preliminary studies showed enhanced accumulation of HuR in the cytoplasmic fraction in some of the breast cancer cells tested. Treatment of three human breast cancer cell lines, MCF-7, MDA-MB-231 and Hs578t, with a siRNA specific to HuR resulted in enhanced tumor cell radiosensitivity. Clonogenic cell survival assay showed the survival factor at 2Gy (SF2) was reduced from 41.15%, 61.4% and 51% in scrambled siRNA (si-Scr) treated cells to 31.01%, 42% and 39% in si-HuR treated MCF-7, MDA-MB-231 and Hs578t cells, respectively. Treatment with si-HuR led to a dramatic reduction in HuR protein expression compared with si-Scr transfected cells.

Our data demonstrates siRNA-mediated knockdown of HuR enhanced the radiosensitivity of human breast cancer cells. Unraveling the molecular mechanisms by which HuR knockdown restores radiosensitivity could lead to improvements in breast cancer radiotherapy.

Novel Small Molecules with Anticancer Activity in Triple Negative Breast Cancer

Presenter: Anja Bastian

[1]Anja Bastian, [1]Jessica E. Thorpe, [1]Bryan C. Disch, Lora C. [1]Bailey-Downs, [2]Aleem Gangjee, [2]Nilesh Ziware, [1]Michael A. Ihnat
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Abstract: Triple negative breast cancer (TNBC) and basal-like breast cancer (BLBC) are two subtypes of breast cancer that are inherently aggressive and metastatic with high recurrence and mortality rates. TNBC as well as most cases of BLBC, lack the growth factor receptor for EGFR-2/Her2/neu and the receptors for estrogen and progesterone. The absence of these receptors renders TNBC and BLBC resistant to conventional endocrine therapy or other available targeted agents. Thus, the treatment options are restricted to a combination of highly cytotoxic chemotherapy agents such as docetaxel and doxorubicin. Therefore, TNBC and BLBC represent an important clinical challenge to develop more effective agents with lower systemic toxicity.

Previously our laboratory, in collaboration, designed a series of small molecule that have combined thymidylate synthase (TS) and receptor tyrosine kinase (RTK) inhibiting activity in a single molecule. A kill-curve comparison of our novel compounds, AG-43 and AG-311, to traditional TS and RTK chemotherapeutic agents, resulted in drastically steeper kill curves. Screening multiple cancer cell lines with these compounds revealed that TNBC and BLBC cells are highly sensitive. Since these cells lack the key RTKs and are inherently resistant to TS inhibitors, a separate mechanism of cell death must be involved. Further mechanistic investigation indicated a rapid induction of necrosis. Twenty minutes after treatment, MDA-MB-435 BLBC and MDA-MB-468 TNBC cells became hyperpermeable to calcium and molecular dyes (size: 400-900Da), indicating plasma membrane compromise. Next, mitochondrial and endoplasmic reticulum disintegration as well as intracellular calcium release was observed prior to necrotic membrane bleb formation. Further, lactose dehydrogenase release, a marker of necrosis, was observed as early as 3 hr after treatment. Since the addition of a membrane channel inhibitor (ex. PPADS) resulted in decreased permeability, membrane blebbing and ultimately cell death, we hypothesize that the proximal target could be a ligand-gated ion channel such as the purinergic P2X7 receptor.

Finally, in vivo studies in two mouse TNBC/BLBC models showed that AG-43 and AG-311 have significantly greater anti-tumor ($p < 0.05$) and more importantly enhanced anti-metastatic activity ($p < 0.05$) with reduced systemic toxicity when compared to current breast cancer therapeutic agents. Since these compounds showed much better activity against tumor growth in vivo as compared to current therapeutic agents, these agents have significant potential to treat TNBC and BLBC.

The JMJD2B Histone Demethylase: Tumor Promoter and Drug Target

Presenter: William Berry

William Berry and Ralf Janknecht
Department of Cell Biology, University of Oklahoma Health Sciences Center

Abstract: Aberrant activation of the canonical Wnt signaling pathway has been implicated in many different types of cancers. The hallmark of this dysregulation is the stabilization of beta catenin, where it is thereby able to translocate to the nucleus and complex with DNA binding cofactors to drive the expression of its target genes such as cMyc, cJun, cyclin D1, etc. A relatively new enzyme JMJD2B (Jumonji C domain-containing protein 2B) is characterized based on its ability to demethylate H3K9me3. H3K9me3 is believed to be enriched at inactive genes and may need to be demethylated to H3K9me1 in order to promote gene expression.

We first sought to determine whether JMJD2B was upregulated in cancer. In order to test this, we performed a western blot of a non-cancer cell line compared to cancer cell lines and probed for JMJD2B. We determined that JMJD2B is upregulated in human cancer cell lines. Furthermore, we performed an in silico analysis of publicly available microarray data and looked at the level of JMJD2B expression in human cancer patients. Similar to what we found in our cancer cell lines, JMJD2B is upregulated. Additionally, we found that JMJD2B and beta catenin interact by co-immunoprecipitation when co-expressed in 293T cells. This was also confirmed by GST-pulldown experiments. To test whether JMJD2B is also a co-activator of beta catenin, we over-expressed JMJD2B in cancer cells and found an increase in luciferase activity with a beta catenin reporter construct, however we did not see this activation with a mutant that lacks demethylase activity. We also noted the opposite when JMJD2B was depleted by shRNA. More importantly, when we depleted cancer cells of JMJ2B, we noticed a significant decrease in proliferation as well as expression of known pro-tumorigenic genes. Our data suggest that JMJD2B is an important cofactor for beta catenin, and that targeting JMJD2B may be beneficial in reducing cancer cell growth.

FAR-RED LIGHT-ACTIVATABLE PRODRUG OF COMBRETASTAIN A-4 USING PHOTO-UNCLICK CHEMISTRY: SYNTHESIS, IN VITRO AND IN VIVO STUDIES

Presenter: Moses Bio, PhD

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Background: Spatio-temporal controlled release of therapeutic agents (drug) is critical to achieve local expression of pharmacological action of drug. One strategy of controlled release that has gained recent attention is the use of light preferably near infra-red (NIR) light. We hypothesized that the release of combretastatin A4 (anti-cancer drug) mediated by singlet oxygen cleavable linker could kill cell with the irradiated area resulting in enhanced antitumor activity and reduced toxicity.

Method: 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-NCLCA4 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. The in-vitro and in-vivo antitumor activity of CMP-L-CA4, CMP-NL-CA4 after NIR laser irradiation was studied. The in-vivo antitumor was evaluated by intraperitoneal injection of prodrug conjugates to bulb C mice bearing subcutaneous xenograph tumor.

Result: In vitro study using MCF-7 cells, the prodrug conjugate CMP-L-CA4 was 20 fold less toxic than parent drug CA4 without NIR laser irradiation IC50D = 200 nM → IC50P =8 nM which is presumably due to the release of CA4. The dark toxicity and photo toxicity of CMP-NL-CA4 was quite similar IC50D: 1802 nM → IC50P = 1063 nM (CMPNCL-CA4) since the release of CA4 is not possible. Most exciting result was that CMPL-CA4 showed better antitumor effects than CMP-NCL-CA4 upon irradiation. The results indicate injection of CMP-L-CA4 followed by NIR irradiation showed significant tumor growth delay compared to CMP-NL-CA4 with NIR irradiation, (CA4 + CMP-OH) with NIR irradiation. The tumor growth delay of CMP-L-CA4 with NIR irradiation may be attributed to the release of CA4 and photodynamic effect (PDT) of CMP-OH.

Conclusion: 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 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.

Cancer Functional Genomics Core

Description: Gene expression variability across the genome has significant impact on understanding the progress and prognosis of cancer. The Cancer Functional Genomics Core at the Stephenson Cancer Center offers cutting-edge technology that can provide extremely accurate and reliable expression data to support drug discovery research. The versatile Agilent SureScan Microarray Scanner system provides the ability to scan genome-wide microarray profiles. The Biorad CFX96™ Touch Real-Time PCR Detection System provides highly-reliable quantitative individual gene transcription profiling. Functional analysis of proteins using biochemical assay can be evaluated with the Perkin Elmer EnVision® Multilabel Reader. Other instruments housed in the facility include the Biorad Experion™ Automated Electrophoresis Station and Agilent 2100 Bioanalyzer.

Core services include:

- Array Scanning and Quantification
- Reverse Proteomics Array (coming March 2013)
- Real-Time PCR
- Multimodal Assay Screening
- DNA/RNA/Protein Purity Analysis on a Chip

MESENCHYMAL STEM CELLS COMBINING HOLLOW SILICA NANOPARTICLES AS TARGET VECTOR TOWARD BREAST TUMOR PHOTOHYNAMIC THERAPY

Presenter: Binrui Cao, PhD

[1]Binrui Cao and Chuanbin Mao
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Abstract: Photodynamic therapy (PDT) combines non-toxic photosensitizer (PS), harmless visible light, and oxygen to generate cytotoxic reactive oxygen species (ROS) for treating cancer cells. However, current PDT is limited by the difficulty in specifically delivering PS to the target site. Recently, it has been reported that mesenchymal stem cells (MSCs) can migrate to tumors and tend to be distributed and retain at the tumors. Therefore, we employed MSC as a carrier to deliver PS to breast tumors for treatment.

We first synthesized porous silica nanoparticles (SiO2NPs) and then loaded purpurin-18 (pP-18) PS into the pores to form PS-loaded SiO2NPs (PS-SiO2NPs). To evaluate the uptake of PS-SiO2NPs by MSCs, we used FITC-labeled peptide-SiO2NP as a substitute and found green fluorescence around cell nuclei, suggesting the internalization of green-dye-loaded SiO2NPs inside MSCs. Then we performed in vitro migration assay and found that the loading of PS-SiO2NPs in MSCs did not significantly reduce the number of MSCs that migrated to MCF-7 cells. To verify the generation of ROS inside MSCs upon the irradiation, a DCFH-DA staining kit was used. Upon light irradiation on MSCs loaded with PS-SiO2NPs, intracellular ROS level was increased with the concentration of PS-SiO2NPs used to interact with MSCs. This fact indicates that the internalization of PS-SiO2NPs in MSCs resulted in the presence of PS in MSCs, which was activated by light to trigger the excitation of oxygen into singlet oxygen.

At last, we performed the in vivo anti-tumor test. We found that the tumor size and weight were reduced in Group 1 compared to Group 2 and 3. This indicates that PDT at day 1 after injection (Group 1) generated ROS to inhibit tumor growth whereas the absence of PS-loaded MSCs (Group 3) did not induce PDT even under light irradiation. H&E staining of tumor tissues of Groups 1 and 3 also verified the death of cells in the tumors in Group 1. It is interesting that PDT at day 5 after injection (Group 2) did not induce additional inhibition compared to PDT at day 1, probably because MSCs co-injected with MCF-7 cells could stimulate and support tumor tissue once they were present in the tumor microenvironments before PDT was applied on Day 5. These results show that PDT needs to be initiated soon after the arrival of MSCs in tumor sites when MSCs are used as a carrier for drug delivery.

In conclusions, we took advantage of the tumor-homing capability of MSCs to deliver PS to cancer cells and tumors. When the PS-loaded MSCs were injected into MCF-7 bearing tumors, the tumor growth was inhibited, suggesting the retention of MSCs (and thus the PS loaded in MSCs) in tumors and the consequent destruction of tumors by PDT.

Implementation of a Community-Based Participatory Research Training to Address Obesity

Presenter: Leslie Carroll

Leslie Carroll
College of Public Health, University of Oklahoma Health Sciences Center

Background: Community-based participatory research (CBPR) is an important component in the process of implementing evidence-based research into practice. The CBPR process can facilitate true community participation and foster academic and community partnerships. Researchers engage in a co-learning process with the community rather than imposing a research protocol on them. This poster presentation reports on the adaptation, implementation, and evaluation of a CBPR training to build the capacity of Native American communities to conduct research addressing obesity. While Native American communities experience significant diet-related health disparities, few culturally appropriate and community-based participatory programs addressing obesity exist within Native communities. This poster reports on a partnership between three Native American communities in Northern California, two local Indian health clinics, and the University of California, Davis, to adapt and implement a CBPR curriculum to facilitate the development of community-directed obesity prevention programs.

Methods: The Developing and Sustaining Community-based Participatory Research Partnerships: A Skill-Building Curriculum, created by the Community-Campus Partnerships for Health was adapted for implementation in three tribal communities in Northern California. The CBPR training was implemented over the course of two years and included interactive and participatory educational sessions. A participatory evaluation component was added to the curriculum, with the community members assessing the efficacy of the training and the community-clinic-academic partnership in building community capacity to conduct research. Both qualitative and quantitative evaluation measures were assessed. To collect qualitative data, the community created a focus group guide, with questions developed through a participatory process, and implemented in three focus group sessions. To collect quantitative data, a survey created by the Native American Research Center's for Health (NARCH) study was implemented. Both the qualitative and quantitative data measured the community members' satisfaction in building positive, trusting, and sustainable relationships with partners and the impact of the project.

Results: Focus groups identified three themes that highlight the training experience: 1) Native communities want a voice in research; 2) the CBPR training gave community members' confidence; and 3) the CBPR training showed community members the importance of telling their community's stories. Surveys revealed that both research infrastructure and capacity were built. These tribal communities are now in the process of creating obesity-focused interventions that are guided by the CBPR principles.

Conclusion: Community-based participatory research (CBPR) shows promise in translating evidence-based research into practice and creating community-directed obesity interventions. The CBPR curriculum built community capacity and infrastructure to create culturally relevant and community-driven interventions.

ROLE OF DCLK1+ STEM CELLS IN EPITHELIAL-MESENCHYMAL TRANSITION AND INTESTINAL NEOPLASIA

Presenter: Parthasarathy Chandrakesan, PhD

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Background: Recent studies indicate that the gain of stem cell-like properties are essential features of Epithelial-mesenchymal transition (EMT). We have demonstrated that doublecortin CAM-kinase-like-1 (Dclk1), a putative intestinal stem cell marker is frequently overexpressed in many cancers and regulates the expression of EMT-associated transcription factors. The functional interdependence between EMT-associated factors and Dclk1 highlights the common mechanism involved in EMT and cancer stemness. However the role of Dclk1 in regulating the onset of EMT and intestinal neoplasia is poorly understood.

Aim: To determine the role of Dclk1 in promoting EMT, stemness and intestinal neoplasia.

Methods: Intestinal epithelial cells isolated from nine month-old $APC^{min/+}$ mice along with their wild-type (WT) littermates were subjected to primary cell culture to identify the onset of EMT. Gene and protein expression of molecular signaling and EMT-factors were analyzed by Western blot and real-time RT-PCR. FACS sorted Dclk1+ cells were used for clonogenic assay to identify self-renewal and neoplastic potential. Selective miRNAs were also quantitated in the present study using real time RT-PCR analysis. Dclk1 small interfering RNA incorporated in nanoparticles (siDclk1-NP) and siScramble-NP were administered to the $APC^{min/+}$ mice and their wild type littermates and the epithelial cells isolated from the small intestine were used to explore the onset of EMT, self-renewal and neoplastic potential and molecular signaling alterations.

Results: Intestinal epithelial cells isolated from $APC^{min/+}$ mice formed monolayer with mesenchymal morphology, suggesting a process of onset of EMT. Dclk1+ cells isolated from the small intestine of $APC^{min/+}$ mice formed an average of 150 spheroids (cystic spheroids) per high power field (HPF) compared to WT (budding spheroids) (14 per HPF). Expression of Notch, β-catenin and NF-κB signaling molecules were increased in the isolated epithelial cells of $APC^{min/+}$ mice. In addition c-Myc, snail and vimentin were increased, with decreased E-cadherin expression in the isolated epithelial cells of $APC^{min/+}$ mice confirmed the onset of EMT and active tumor progression. Notably, we observed increased expression of Dclk1 in the epithelial cells, and interestingly Dclk1+ spheroids derived from the small intestine of $APC^{min/+}$ mice, showed increased EMT and oncogenic signals. These results suggest that loss of APC upregulates Dclk1 expression and onset of EMT, considered as driving force for the intestinal neoplasia and metastasis. Knockdown of Dclk1 expression in APC mutant mice efficiently abrogates intestinal adenoma and eliminates the process of EMT.

Conclusion: These data taken together provide support for a critical role of Dclk1 in inducing EMT and promoting intestinal tumorigenesis via a mechanism that involves loss of APC and enhanced stemness.

REDUCED EXPRESSION OF ALDO-KETO REDUCTASE FAMILY 1 MEMBER C3 (AKR1C3) IN NEUROENDOCRINE CELLS AND NEUROENDOCRINE TUMORS IN THE AREODIGESTIVE TRACT

Presenter: Theodore Chang, MD

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Background: Human aldo-keto reductase family 1 member C3 (AKR1C3) is a critical enzyme in androgen metabolism. Interestingly, it possesses many other important catalytic functions including metabolism of other steroids, 11-ketoprostaglandin reductase activity, metabolism of prostaglandins and dihydrodiol dehydrogenase x (DDx), and metabolism of xenobiotics. Previously, we demonstrated AKR1C3 in adenocarcinoma and squamous cell carcinoma but not in small cell carcinoma of lung. In this study, we survey its distribution in normal and neoplastic neuroendocrine and non-neuroendocrine cells of the areodigestive tract.

Design: AKR1C3 and synaptophysin (as neuroendocrine marker) expression were demonstrated by single and double immunohistochemistry in normal tissue, neuroendocrine tumors, and adenocarcinomas from bronchus, pancreas, stomach, small intestine, appendix, and colon. Staining intensity was graded as negative, weak, moderate, or strong. Extent of immunoreactivity was scored as: 0 (negative), 1 (positivity 5%), 2 (positivity >5% to 25%), 3 (positivity >25% to 75%), 4 (positivity >75% to <100%), and 5 (positivity is 100%). Lung adenocarcinomas were studied previously and were not included.

Results: AKR1C3 was demonstrated by immunohistochemistry in pancreatic ducts but not in pancreatic acini or islets, strong expression in superficially located mucosal epithelial cells, weak expression in deeply located epithelial cells such as Brunner's gland, no expression by mucosal associated neuroendocrine cells, and an overall, weaker immunoreactivity in colonic epithelium compared to small intestinal mucosal cells. Out of the 47 neuroendocrine tumors (lung-14, pancreas-10, stomach-2, small intestine-6, appendix-9, colon-6), positive immunoreactivity was found in 6 tumors (12.8%) (lung-2, stomach-1, small intestine-2, colon-1). Out of the 42 adenocarcinomas (stomach-9, colon-9, pancreas-24), positivity immunoreactivity was noted in 40 tumors (95.2%) (2 colonic adenocarcinomas were negative).

Conclusion: Our results suggest the use of AKR1C3 as an adjunct marker to distinguish neuroendocrine tumors from adenocarcinomas. The biogical significance of AKR1C3 expression is uncertain. With its diverse functions, AKR1C3 is likely to play a role in pathogenesis of non-neoplastic and neoplastic diseases, and response to cancer therapy.

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

Presenter: Patricia Coutinho de Souza

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Abstract: Gliomas are the most frequent form of adult primary brain tumors. OKN-007 (2,4-disulfophenyl-PBN) is a nitrone 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), glutamine (Gln), glutamate (Glu), myo-inositol (mIns), N-acetyl aspartate (NAA), taurine (Tau), total lipids and macromolecules at 1.3 ppm (MM14+Lip13a+Lip13b) and at 0.9 ppm (MM09+Lip09). There was a significant decrease in the Lip1.3 peak in OKN-007-treated gliomas compared to untreated gliomas (p=0.049). The results of this study demonstrate that OKN-007 could affect tumor metabolism, which was denoted by significant changes in major metabolite concentrations in lipids in F98 glioma model following treatment. Furthermore, 1H MRS, along with conventional MRI, is a useful method to assess and follow the response of the F98 glioma model treated with OKN-007.

Molecular MRI Differentiation of VEGFR2 Levels in Four Different Experimental Anti-Glioma Therapies within a GL261 Mouse Model

Presenter: Patricia Coutinho de Souza

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Abstract: Angiogenesis is essential to tumor progression and the precise imaging of the angiogenic marker vascular endothelial growth factor receptor 2 (VEGFR2) would provide an accurate evaluation for angiogenesis during a therapeutic response. In this study, we evaluated the molecular MRI differentiation of VEGFR2 levels in untreated gliomas and four different anti-glioma therapies in a GL261 mouse model that included three experimental compounds (the nitrone OKN007, two different synthetic ubiquitin inhibitor peptides, and a combined therapy including OKN007 + ubiquitin inhibitor peptide). The expression of VEGFR2 was evaluated by using an anti-VEGFR2-albumin-Gd (gadolinium)-DTPA (anti-VEGFR2) probe with molecular magnetic resonance imaging (MRI). For the peptide 1 treatment group VEGFR2 levels were significantly increased in the tumor region, compared to untreated tumors. For peptide 2, VEGFR2 was significantly decreased in tumors, compared to untreated tumors. For OKN007, VEGFR2 was significantly decreased in tumors, compared to untreated tumors. When OKN007 and peptide 2 were combined, there was also a significant decrease in VEGFR2 levels in tumor regions, compared to untreated gliomas. Our study confirmed that in vivo VEGFR2 levels can be monitored as a function of therapeutic evaluation.

COHESION FATIGUE: CHROMATID SEPARATION IN THE ABSENCE OF COHESIN CLEAVAGE

Presenter: John Daum

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Abstract: During chromosome duplication in S phase, the cohesin complex is loaded upon and provides cohesion between homologous sister chromatids until the onset of anaphase in mitosis. Cohesion resists the pulling forces generated by the mitotic spindle and allows the cell to orient paired sister chromatids such that each individual chromatid will form interactions with microtubules emanating from opposing centrosomes of the mitotic spindle. At the transition from metaphase to anaphase, cohesion is lost and individual chromatids proceed to opposite poles of the cell ensuring that both daughter cells receive the appropriate complement of chromosomes. During this transition, the loss of cohesion is accompanied by the cleavage of SCC1/RAD21, a component of the cohesin complex. Accordingly, the strict regulation of cohesion by the cohesin complex is critical for the maintenance of ploidy. Recently, we described a phenomenon termed cohesion fatigue that occurs when cells are delayed at metaphase wherein paired sister chromatids separate from each other prior to the regulated cleavage of SCC/RAD21 and the onset of anaphase. We isolated chromosomes from mitotic cells that had undergone cohesion fatigue and from cells with intact sister chromatid cohesion. Surprisingly we found little difference between levels of SCC1/RAD21 and other cohesin complex members associated with paired sister chromatids and the amounts associated with separated individual chromatids. Therefore it is possible to loose sister chromatid cohesion without cleaving SCC1/RAD21 and without observable loss of chromosome-associated cohesin complex. Cohesion fatigue proceeds asynchronously within cells and evidence of fatigue, noted by abnormal increases in distances between paired sister centromeres, is apparent in a subset of chromosomes when the duration of metaphase is increased only two to threefold. This condition can arise spontaneously in a subset of untreated cells as they attempt to form appropriate centromere-microtubule interactions. We postulate that the earliest elements of cohesion fatigue may induce inappropriate centromere-microtubule attachments by spatially altering the intracentromeric components responsible for forming and maintaining correct interactions. Cohesion fatigue may cause additional delays in mitotic progression, lagging chromosomes during anaphase, centromere fission, or the generation of micronuclei. These errors are implicated in the failure to maintain ploidy during mitosis and meiosis and in carcinogenesis.

PERCEIVED BARRIERS TO HPV VACCINATION BY AMERICAN INDIAN TEENS AND CAREGIVERS

Presenter: Valerie Eschiti, PhD, RN, AHN-BC, CHTP

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Background: Incidence and mortality rates due to cervical cancer are higher in American Indians (AIs) than Whites in US. Although the human papilloma virus (HPV) vaccine is available to prevent cancers resulting from HPV infection, completion rates of HPV vaccine series for AI's is low for those ages 9-18 years in the Oklahoma and Nashville areas of Indian Health Service (IHS), especially for completion of the 3-vaccine series. Barriers to obtaining the vaccine are unknown; some may be culturally bound. Since infection with HPV is primary cause of several cancers, underutilization of vaccine may lead to continued cancer disparities in the AI population.

Purpose/Objective: To determine perceived barriers to HPV vaccination by AI youth and caregivers among AIs in Comanche Nation and Poarch Creek Band of Indians (Alabama-located within Nashville area of IHS).

Methods: Using Unitary Appreciative Inquiry as a framework, a community-based participatory research approach was utilized to develop the proposal and conduct the study. This qualitative, descriptive study was conducted using focus groups of key informants with AIs of Comanche Nation and Poarch Band of Creek Indians with youth ages 13-15 and 16-18 years, as well as caregivers of youth, ages 9-18 years. Sessions were audiorecorded, data transcribed, and coding scheme and themes were developed using content analysis.

Results: The sample size is 63 teens and adults. Preliminary themes are emerging, indicating a lack of awareness of HPV virus and vaccination, in part due to a history of cultural taboos regarding speaking of sexual matters in the home. Data is being analyzed, and will be completed by March 1, 2013.

Conclusions and Implications: We will have conclusions and implications to share after completion of data analysis. Preliminary findings reveal a need and desire among Comanche adults and teens to become more knowledgeable about HPV and the vaccine.

CANCER-RELATED EDUCATION AND GOAL ATTAINMENT IN COMANCHE NATION

Presenter: Toni Finch, MSN, RN, OCN

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Background: The Southern Plains (Oklahoma, Texas, and Kansas) Native Americans (NAs) have excessive cancer incidence and mortality rates. Despite implementation of educational strategies that have successfully reached many racial/ethnic groups, this is not the case among NA people in the Southern Plains. Native navigation is a strategy of employing trained Native individuals to assist other Natives to navigate the health care system to receive needed education and services.

Purpose/Objectives:

1. To determine to what extent Native Navigator-initiated NA community education workshops will improve knowledge regarding cancer prevention, screening, and treatment among NA participants.

2. To determine whether demographic variables of age, education, and annual family income in NA participants attending Native Navigator-initiated community education workshops are associated with pre- and post-test scores on cancer-related knowledge items developed for NAs.

3. To determine if goal setting based on Goal Attainment Scaling (GAS) will be an effective method for participants in community cancer education to make progress in cancer-related behavioral change.

Method: This three-year multidisciplinary project (nursing, public health, and statistics) employed a community-based participatory approach using mixed methods to examine use of Native navigators to deliver community cancer education workshops as an intervention in the Comanche Nation. Goal setting was implemented with NA participants in community cancer education workshops as a means of assisting NAs to make progress towards achieving cancer-related behavior change.

Results: We will present quantitative findings from one year of data collection at two sites in Comanche Nation. There was outstanding interest by community members, with 125 participants in the first year of community workshops; this exceeds recruitment expectations. Data analysis is currently being conducted, and will be completed by March 1, 2013.

Conclusions and Implications: Those in Comanche Nation are receptive to culturally tailored cancer educational workshops which incorporate individual goal setting. At completion of data analysis, we will have conclusions and implications to share. Preliminary analysis indicates an increase in cancer knowledge and mixed results with goal setting for participants.

EXAMINING THE CHEMICAL CONSTITUENTS OF SECONDHAND VAPOR

Presenter: Steven B. Foster, PhD

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Abstract: Many municipalities, workplaces, and airlines are banning the use of e-cigarettes (ECs) due to fear that the secondhand vapor (SHV) emitted from the user may have dangerous chemical constituents that could negatively affect non-users. Little is known about the chemical constituents of SHV as they are just now being explored. With this in mind, we sought to examine the presence and the amount of Nicotine, Glycerin, Diethylene Glycol, Ethylene Glycol and Propylene Glycol (PG) in SHV and secondhand smoke (SHS). 20 smokers, naïve to ECs, were recruited as part of a clinical laboratory trial; 18 completed four sampling sessions, each separated by 1-hr, following a 12-hr abstinence from smoking. 3 popular brands of ECs (bluCig, ProSmoke, SmokeTip) and participants' own brand of cigarette (OBC) were sampled in a counterbalanced fashion. After completing paper-and-pencil measures and spirometry, participants vaped/smoked for 5 minutes. After 2 minutes of vaping/smoking, participants would inhale and then exhale the vapor/smoke into a modified 1 L glass Erlenmeyer flask. After methanol extraction, the liquid was analyzed by gas chromatography mass-spectrometry. Reported values are the average of 18 participants and are based on integrated spectral areas, concentrations which correspond to those generated by standard curves produced from commercial standards of each compound. SHV from SmokeTip contained the highest level of PG, 17.03 micro-M. Despite advertisements that bluCig and ProSmoke do not contain PG, SHV bluCig and ProSmoke contained 1.07 micro-M and 6.61 micro-M, respectively. In OBC the PG levels were 1.40 micro-M. Nicotine levels were highest in SHS (1.11 micro-M), while nicotine levels in SHV varied based on EC product and strength. Of the ECs, nicotine was lowest in bluCig Light SHV (0.10 micro-M) and highest in SmokeTip Full Flavor SHV (0.45 micro-M). bluCig had the highest level of glycerin, 382.45 micro-M, with OBC the lowest at 43.73 micro-M. Glycerin levels in ProSmoke and SmokeTip were 179.31 and 287.85 micro-M, respectively. No ethylene glycol or diethylene glycol was detected in any of the SHV samples.

EWI-2/PGRL INHIBITE CANCER CELL MOTILITY VIA DOWNREGULATION OF EPITHELIAL- MESENCHYMAL TRANSITION

Presenter: Chenying Fu, PhD

Chenying Fu, PhD
Department of Physiology, University of Oklahoma Health Sciences Center

Abstract: Tumor suppressor EWI-2/PGRL physically associates with tetraspanins and regulates integrins and impaires cancer cell proliferation and movement such as cancer cell migration and invasion. EWI-2 is a member of subfamily of Ig proteins and expressed in different tissues such as brain, peripheral blood lymphocytes, hepatocytes and prostate etc. In this study, knocking down EWI-2 in PC3 prostate cancer cell line does not promote wound healing but can increase cell migration on fibronectin-coated substratum, indicating that EWI2/PGRL directly regulates cell migration. Invasion assay on metrigel shows more invasive cells in EWI-2 knocking down group. Interestingly, western-blot data showes up vimentin expression level is upregulated after knocking down EWI-2 in PC3 prostate cancer cell line which indicates cells went through epithelial–mesenchymal transition. This phenomenon is also oberserved in DU145 prostate cell line but not in U87 glioma cell line. Immunofluerencent staining showes after knocking down EWI-2, cell-cell junction become weaker and cell morphology is thinner and longer. Cell-cell adhesion assay indicated less and smaller cell-cell aggregation formation. Cell-metrix adhesion assay showes more attached cells on fibronectin coated plastic in knocking down group. In conclusion, EWI-2/PGRL can inhibit cancer cell motility via the downregulation of epithelial–mesenchymal transition.

PADDA, A NOVEL ASSAY TO CHARACTERIZE MAINSTREAM AND SIDESTREAM SMOKE INDUCED DNA DAMAGE

Presenter: Vengatesh Ganapathy, PhD

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Introduction: Cigarette smoking is the leading cause of preventable death in the United States. An estimated 45.3 million people in the United States smoke cigarettes. When a cigarette is smoked, roughly half of the smoke generated is sidestream (SS) emitted from the smoldering end of the cigarette and the other half exhaled is mainstream (MS). It is estimated that up to ~60% of non-smokers are exposed to second-hand cigarette smoke. Second-hand smoke exposure causes serious disease and death. Second-hand smoke is composed primarily (~90%) by the SS and ~10% of MS smoke. SS and MS smoke are complex mixtures of over 4000 chemicals, including more than 50 carcinogens and 200 toxicants. While SS and MS are qualitatively similar with respect to chemical composition, many carcinogens are present in greater amounts in SS than in MS smoke. This suggests that passive smoking may produce effects that differ from those induced by active smoking. Cigarette smokers have increased levels of DNA damage. However, it is still unclear whether second-hand smokers have higher levels of DNA damage than non-smokers. Recently, we filled a major methodological gap by developing a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA) to map and quantify in vivo levels of DNA damage. We have shown that PADDA discriminates several levels of in vivo tobacco-induced DNA damage. Here, we determined the levels and location of DNA damage induced by MS and SS smoke in human oral cells, one of the main targets for tobacco-induced cancer.

Aims:

(1) To define the levels of DNA damage induced by MS and SS smoke in human oral cells.

(2) To determine if persistent nucleotide damage at p53 induced by MS and SS co-localizes with cancer mutational hotspots.

Methods: PADDA was used on a high-throughput setting to quantify DNA damage in SCC-1 oral cells exposed to different doses of MS and SS smoke. Damage localization was identified by f-PADDA. Data were analyzed by Student's t test, chi-square goodness of fit and exact non-parametric tests.

Results: Our data documented PADDA's ability to detect DNA damage in both transcribed strand and non-transcribed strand in human oral cells exposed to MS and SS smoke. There was a significant increase in DNA damage in cells exposed to both MS and SS smoke. Interestingly, we observed significant differences in the levels of DNA damage induced by MS and SS smoke.

Conclusion: Using our novel assay PADDA, we documented for the first time that both MS and SS smoke induced significant levels of DNA damage in human oral cells. This observation is of major clinical importance and reinforces the need for additional tobacco regulation to prevent or reduce the exposure of non-smokers to second-hand smoke. Studies are on-going to characterize the localization of SS smoke induced DNA damage in p53 nucleotides and to quantify the levels of tobacco-induced DNA damage in second-hand smokers.

THE gep PROTOONCOGENE Gα12 MEDIATE LPA-STIMULATED ACTIVATION OF CREB IN OVARIAN CANCER CELLS

Presenter: Ji Hee Ha, PhD

Ji Hee Ha, Jeremy Ward, Lakshmi Varadarajalu1, and Danny N. Dhanasekaran
The University of Oklahoma Health Sciences Center

Abstract: Lysophosphatidic acid (LPA), plays a critical role in the pathophysiology of ovarian cancers. Our previous studies have shown that LPA stimulates the proliferation of ovarian cancer cells through *GNA12*, the *gep* protooncogene $G\alpha_{12}$. The present study is focused on identifying the $G\alpha_{12}$-dependent mechanism through which LPA stimulates the proliferation of ovarian cancer cells. Using ovarian cancer cells in which the expression of $G\alpha_{12}$ is silenced, we demonstrate here that $G\alpha_{12}$-dependent mitogenic signaling by LPA involves the atypical activation of the transcription factor, cAMP-response element binding protein (CREB). Protein/DNA array analyses using LPA-stimulated Hey8 cells in which the expression of $G\alpha_{12}$ was silenced indicated the potent but $G\alpha_{12}$-dependent activation of CREB by LPA. After validating the array data with immunoblot analysis using antibodies specific to Ser133-phosphorylated active form of CREB, we demonstrate that the expression of the constitutively activated mutant of $G\alpha_{12}$ stimulate the activation of CREB even in the absence of LPA whereas silencing of $G\alpha_{12}$ abrogates such LPA-stimulated activation in multiple ovarian cancer cell lines. Furthermore, our results indicate that the robust activation of CREB by LPA is an early event, which can be monitored upon LPA stimulation from 3 minutes onwards. In addition, we establish that LPA/$G\alpha_{12}$-dependent activation of CREB involves an atypical cAMP-independent mechanism involving Ras and ERK. More significantly, our findings indicate that the expression of the dominant negative mutant of CREB (S133A) leads to a reduction in LPA-stimulated increase in Cyclin A levels along with an attenuation of LPA-stimulated proliferation of these cells. Thus, these studies unravel a novel $G\alpha_{12}$-dependent mechanism involving CREB through which LPA stimulates the proliferation of ovarian cancer cells.

TARGETING SINGLE-WALLED CARBON NANOTUBES FOR THE TREATMENT OF BREAST CANCER USING PHOTOTHERMAL THERAPY

Presenter: Roger Harrison, PhD

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Abstract: This project focuses on a new way of targeting single-walled carbon nanotubes (SWNTs) for the treatment of breast cancer with minimal side effects using photothermal therapy. The human protein annexin V (AV) is known to bind with high affinity to phosphatidylserine (PS) in phospholipid bilayers, and AV binds to PS expressed externally on tumor cells and on endothelial cells of the tumor vasculature, but not normal endothelial cells. SWNTs were functionalized by non-covalent attachment to AV using a linker containing polyethylene glycol. A 2 hour incubation with the SWNT-AV conjugate with proliferating endothelial cells followed by washing and 200 seconds of near-infrared (NIR) irradiation at a wavelength of 980 nm and power of 1 watt/cm2 was enough to induce significant cell death, without significant damage to these cells with the irradiation or the conjugate alone. Administration of the same conjugate i.v. in immune-competent BALB/cJ female mice with implanted 4T1 murine mammary tumors resulted in detectable accumulation of the SWNTs in tumor tissues, 24 hours post-administration. 4T1 tumor cells are highly metastatic in mice and share many characteristics with human mammary carcinomas. A conjugate dose of 0.8 mg SWNT/kg administered i.v. in BALB/c female mice and followed 1 day later by NIR irradiation of the tumor for 175 seconds at a wavelength of 980 nm and power of 1 watt/cm2 led to complete disappearance of implanted 4T1 mouse mammary tumors for the majority of the animals by 11 days after irradiation treatment. The combination of the photothermal therapy with the immunoadjuvant cyclophosphamide, administered at a low dose 2 days hours irradiation, resulted in increased survival. The in vivo results suggest the treatment is a promising approach to treat breast cancer with minimal side effects.

NUCLEOSIDE TRANSPORTER FUNCTION IN CANCER THERAPY

Presenter: Franklin A. Hays, PhD

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

Introduction: The human equilibrative nucleoside transporter (hENT) modulates pancreatic cancer therapeutic efficacy by serving as a cellular gatekeeper to nucleoside-derived (e.g., gemcitabine) drug absorption. Higher hENT expression levels, absence of hENT mutations, and homologous hENT expression profiles in tumors have been strongly correlated with longer survival in gemcitabine-treated pancreatic cancer patients. Unfortunately, very little is known about the molecular basis for how nucleoside-analog therapeutics are internalized by cells and the manner in which their efficacy is modulated by membrane resident transporters such as hENT. No structural data is currently available for this family. In addition, no functional assays using purified protein have been published making functional analysis difficult. Our efforts are focused on 1) developing novel functional assays using purified protein to characterize nucleoside transporter function and 2) determining 3-dimensional nucleoside transporter structures to guide future drug discovery and development. Results outlined in this poster describe our progress in pursing molecular structure of the sensitive (hENT1) and insensitive (hENT2) isoforms as well as progress in developing *in vitro* proteoliposome assays for these proteins.

ELIMINATING TOBACCO-RELATED CANCER HEALTH DISPARITIES IN OKLAHOMA WORKPLACES: A QUALITATIVE POLICY EVALUATION

Presenter: Angela Helt MA and Arian Davis

[1]Angela Helt, MA, [1]Arian Davis, and [2]Jessica Blanchard, PhD
[1]Department of Anthropology, University of Oklahoma, [2]Center for Applied Social Research, University of Oklahoma

Abstract: This poster addresses issues related to the implementation and evaluation of comprehensive policies aimed at the reduction of cancer and other tobacco-related health disparities through the elimination of tobacco use in workplace environments. In February of 2012, Governor Mary Fallin signed Executive Order 2012-01 mandating all state properties become tobacco free environments, making Oklahoma the first state to make all state properties 100% tobacco-free both indoors and outdoors. Researchers from the University of Oklahoma conducted a series of twelve semi-structured interviews with representatives from eleven pre-selected stage agencies to evaluate the planning, implementation, and perceptions of tobacco-free policies in the workplace as a result of the Executive Order. State agency representatives were asked a series of questions pertaining to the recent passage of the Executive Order, including questions related to agency-specific policies and procedures, attitudes and perceptions, compliance and violations, behavioral and other outcomes, ease of facilitation, and barriers impacting implementation. All interview data was transcribed and coded according to pre-determined and emergent themes, and the final content analysis was supplemented with data derived from ethnographic observations, field notes, and photographic accounts.

Our preliminary evaluation suggests that the implementation of the executive order has directly contributed to the reduction of tobacco use on state property, thereby reducing exposure to second-hand smoke at most state workplaces. We also found that the implementation of the Executive Order altered the use of workspaces and the nature of employee interactions in ways that both facilitated and undermined the stated intent of the Executive Order. We will present some strategies, based on our own findings and on recommendations from interviewees, for developing more productive and impactful ways to implement comprehensive tobacco use policies within diverse agency structures.

HOW CD82 INHIBITS CANCER CELL MIGRATION FROM CHOLESTEROL BINDING MOTIF TO MEMBRANE THERMODYNAMICS

Presenter: Chao Huang

Chao Huang
Department of Physiology, University of Oklahoma Health Sciences Center

Abstract: CD82, a member of the tetraspanin family, is a cell membrane molecule expressed in all multicellular eukaryotes, it has 4 transmembrane regions and 2 extracellular loops and one intracellular loop. Generally CD82 is considered to be the molecular scaffold which can interact multiple molecules and regulate their functions, and it was discovered that the expression of CD82 is negatively correlated with the progression of prostate cancers, when prostate cancer cells become aggressive or migrative, the expression of CD82 is generally lost. However, the mechanism by which CD82 inhibits cancer cell migration is still unknown.

In this project, we hypothesize that CD82 has a cholesterol binding motif which can bind to cholesterol and facilitate molecular interaction on the membrane and become part of the membrane lipid raft. Since cholesterol content of the cell membrane determines the fluidity of cell membrane, when CD82 binds to cholesterol the fluidity of CD82 and other relative molecules decrease, thus gives a chance for these molecules to collaborate and to form the lipid raft to exert functions. So, by simply altering the cholesterol binding motif, it is possible to change the pattern of molecular interactions on the cell membrane and the signals are altered, which may alter the functions of this migrations inhibitory molecule.

CATEGORIZATION OF CIN CATEGORIZATION LESIONS ACCORDING TO IMMUNOHISTOCHEMISTRY AND HPV GENOTYPE

Presenter: Sanam Husain, MD

Sanam Husain, Rosemary Zuna.
Pathology Department, University of Oklahoma Health Sciences Center. Oklahoma City, Oklahoma

Background: Follow-up for women with CIN lesions is largely dependent on the histologic grade of the lesion. Reproducible criteria for pathologic interpretation are needed to insure optimal patient care. In this pilot study, we evaluate the use of immunohistochemical stains for p16 and Ki67 to 1) assist in reproducible interpretations of these lesions; 2) identify the relationship of HPV genotype with CIN histology.

Design: Histologic sections of 55 CIN lesions of known singleton HPV type were categorized by H&E using a score derived from three independent blinded pathologist interpretations. Replicate slides stained with p16 and Ki67 were interpreted blindly by two pathologists using a standardized protocol. The final score for each test was the sum of both pathologists' results. All interpretations were performed without knowledge of the HPV results. Two tests for p16 were generated by each pathologist: 1) score based on the highest epithelial level (thirds) of positive staining [PH]; 2) pattern score [PI] based on the intensity of the p16 stain for each third of the epithelial thickness. Ki67 was evaluated by the 1) highest level (third) of positive nuclei [KH] and 2) estimated percentage [KP] of positive nuclei in the lesion. These results were evaluated in the context of the histologic diagnosis (score) and HPV genotype.

Results: Final diagnoses based on score showed 11 CIN1, 17 CIN2, 27 CIN3. There was high correlation between diagnosis and p16 staining (PH and PI, each $p < .001$, Fisher's Exact Test), and with Ki67 (KH, $p < .001$), and (KP, $p < .001$). HPV16 was found in 2 (6.9%) CIN1, 8 (27.6%) CIN2, 19 (65.5%) CIN3; carcinogenic (not HPV16) genotypes in 3 (16.7%) CIN1, 9 (50.0%) CIN2, 6 (33.3%) CIN3; and non-carcinogenic genotypes in 6 (75.0%) CIN1, 0 CIN2, 2 (25.0%) CIN3 ($p < .001$). While the p16 and Ki67 data for each case (even within HPV genotype) typically mirrored the histologic diagnosis, these data suggest an association of genotype with diagnosis.

Conclusion: These results support the use of this protocol in a larger study to categorize CIN lesions. This approach shows promise to help standardize the interpretation of CIN lesions among pathologists and clarify the significance of CIN2. Similarly, there was an association of HPV genotype with diagnosis and immunohistochemical results that may give insight into the biological potential of these lesions.

Formulation and characterization of SHetA2 capsules for phase 0 clinical trials

Presenter: Mariam Ibrahim

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Aim: In preclinical studies, oral administration of SHetA2, a novel anti-cancer compound, with kolliphor inhibited development and sizes of tumors in Rat MNU mammary cancer and APCmin/+ mouse models. No adverse reactions to this drug were determined in formal toxicological studies supporting advancement to clinical trials. The aim of this work was to prepare SHetA2 capsules for human use in Phase 0 studies.

Methods: Its suitability as vehicle in hard gelatin capsules was studied by filling kolliphor in three states in capsules and observing them for 7 days at 25°C. Rifampicin was used as a model since it has similar physicochemical properties to SHetA2. Rifampicin-kolliphor capsules were prepared by either dispersion of the drug in the melted Kolliphor or by drug levigation with semisolid kolliphor. Uniformity of drug content within a capsule batch was determined by UV. Dissolution of drug from each capsule was determined by the US Pharmacopeia method. The critical micelle concentration (CMC) of kolliphor in these formulations was determined as this is the mechanism of increased SHetA2 solubilization and bioavailability.

Results: The shape and integrity of hard gelatin capsules filled with Kolliphor in different states with or without rifampicin was intact over the 7 day observation period. Capsules filled with the drug dispersion in melted kolliphor had a drug content of 96.67±9.82 mg and the drug was 100% dissolved within 2 hours, whereas capsules prepared by levigation had a drug content of 77.47±34.5 mg and 100% of the drug was dissolved from the capsule within 3 hours. The CMC concentration of Kolliphor was 0.025% which is well within the concentration used in both capsule formulations. Thus, the drug in capsules and in solution should be equivalent.

Conclusion: Formulation of SHetA2 using melted Kolliphor in hard gelatin capsules appears suitable for use in Phase 0 clinical trials.

Molecular Imaging Core

Description: The Molecular Imaging Core provides non-invasive optical imaging services to Stephenson Cancer Center members and other investigators at the OU Health Sciences Center and neighboring institutions. The Core includes the following equipment:

- IVIS Spectrum Imaging System – provides a wide range of imaging capabilities including bioluminescence, fluorescence, and near-infrared imaging with 3D anatomical overlay
- Carestream In-Vivo Xtreme Imaging System – specifically designed for researchers seeking high-sensitivity luminescence, fluorescence, radioisotopic, and radiographic imaging
- Leica Fluorescence Stereo Microscope
- INVIVO 400 and 500 Hypoxia Workstations

Core services include:

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

ROLE OF GONADOTROPHINS ON INTESTINAL TUMORIGENESIS

Presenter: Naveena B. Janakiram, PhD

Naveena B. Janakiram, PhD
Department of Medicine, University of Oklahoma Health Sciences Center

Abtract: Colorectal cancer is the third most common cancer diagnosed in both men and women in the United States. The American Cancer Society's estimates for the number of new colorectal cancer cases in the United States for 2013 are 142,820. Use of fertility drugs have reported to decrease overall cancer risk. Whereas, a recent study in younger women (~24yrs) who went through fertility treatments showed greater risk of developing breast cancer and reported to have increased estrogen levels. These conflicting reports on fertility drugs and possible role of estrogen in colon physiology suggested investigation of fertility drugs having any crosstalk with estrogen signaling in colon carcinogenesis. Gonadorelin an analog of GnRh (gonadotrophin releasing hormone) stimulates the synthesis and release of luteinizing hormone (LH) and Follicle-stimulating hormone (FSH). GnRH and its receptor play an important role in the regulation of cellular functions in an autocrine or paracrine manner, in addition to regulating the secretion of gonadotropins. Estrogens, through ER receptors are reported to have organization and architectural maintenance of the colon. Experiments were designed to evaluate gonadorelin (150ng/animal, 5 subcute injections/week for three alternate weeks) and raloxifene (an ER receptor modulator, 1ppm in diet) individually or in combinations (simultaneously or gonadorelin injections followed by raloxifene treatment) for their role in intestinal tumorigenesis using 6 week old female APC$^{Min/+}$ mice to understand if they interact to alter their functions during colonic tumorigenesis. After 14 weeks of treatment these mice were killed to analyze and enumerate intestinal tumors. As per our experimental evidence, we observed gonadorelin and raloxifene to inhibit colon carcinogenesis (>70% $p < 0.01$ and >75% $p < 0.01$ respectively) in Apc$^{Min/+}$ mice. We have also observed a significant decrease in small intestinal polyps both in their size and number. Importantly, the treated colonic tumors showed significant inhibition of stem like cell markers (Lgr5, CD44 and Epcam) compared to untreated colon tumors. Further combinations of these two drugs administered simultaneously and/separately showed significant colonic inhibition compared to control mice. Interrelation between these two signaling pathways was observed when the respective drugs were administered simultaneously. A detailed mechanism involved for these observations will be discussed.

PATTERNS OF CARE FOR LOCALIZED BREAST CANCER IN OKLAHOMA 2003-2006

Presenter: Amanda Janitz, MPH

[1]Janis E. Campbell, PhD; [1]Sara Vesely, PhD; [1]Amanda Janitz, MPH; [2]Dana Lloyd, MS, RHIA, CTR; [3]Anne Pate, PHD
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Abtract: Breast cancer is the most commonly diagnosed cancer among women in the US and Oklahoma with over 250,000 diagnosed in the US and 3,000 in Oklahoma in 2009. Despite well-established clinical guidelines for breast cancer treatment, standard of care in breast cancer treatment remain far from universal in the United States. The purpose of this study was to describe the extent to which patients receive guideline-based, stage-specific treatments for localized female breast cancer as defined by the National Comprehensive Cancer Network, also referred to as Standard of Care (SOC) in Oklahoma and determine if there were differences by treatment and demographic factors.

Data were obtained from the Oklahoma Central Cancer Registry from 2003 through 2006. We included localized, invasive female breast cancers in this study and analyzed both treatment and demographic factors. We used the National Comprehensive Cancer Network treatment guidelines to determine whether SOC was met, either a modified radical mastectomy (MRM) or breast conservative surgery (BCS) followed by radiation therapy. Among women who received BCS, we used logistic regression to evaluate the association between demographics and whether or not the patients met SOC.

In Oklahoma, 91% (95% CI: 90%, 92%) of the 2003-2006 localized breast cancer patients were treated with the recognized SOC. All of those receiving MRM met SOC. Of those receiving BCS with radiation therapy, 87.2% met SOC (95% CI: 85.9%, 88.5%). Among women receiving BCS, women 75 years and older (OR=0.22, 95% CI: 0.17, 0.30) as compared to younger women and women living in non-metro areas (OR=0.78, 95% CI: 0.61, 0.99) as compared to women living in metro areas had lower odds of meeting SOC. Insurance also impacted whether SOC was met. Women with Medicare/Medicaid (OR=0.31, 95% CI: 0.23, 0.43), Medicaid (OR=0.46, 95% CI: 0.25, 0.83), Medicare (OR=0.38, 95% CI: 0.29, 0.51), or those not insured (OR=0.29, 95% CI: 0.16, 0.52) had lower odds of meeting SOC as compared to women with private insurance.

Overall, 91% of women met SOC for their localized breast cancer treatment. Demographic factors such as age, residence (metro vs. non-metro), and insurance type are associated with meeting SOC among women who received BCS.

This work was performed at the Oklahoma State Department of Health and the University of Oklahoma Health Sciences Center, College of Public Health, Department of Biostatistics and Epidemiology. The authors request this work be considered for a poster presentation.

CONGENITAL ANOMALIES AND CHILDHOOD CANCER IN OKLAHOMA: A LINKAGE ANALYSIS

Presenter: Amanda Janitz, MPH

[1]Amanda E. Janitz, MPH, [1]Barbara R. Neas, PhD, [1]Janis E. Campbell, PhD, [2]Anne Pate, PhD, [2]Renee Powell, MPH
[1]Department of Biostatistics and Epidemiology, College of Public Health, [2]Oklahoma State Department of Health

Abtract: Several data-linkage studies found an association between congenital anomalies and childhood cancer. However, this linkage has not been done in Oklahoma using the existing birth defects and cancer registries. The results of this linkage may generate hypotheses about common pathways of congenital anomalies and cancer. We aimed to understand the process of data-linkage between these registries and determine if there was an association between congenital anomalies and childhood cancer.

Data were obtained from the Oklahoma State Department of Health from the Oklahoma Birth Defects Registry (OBDR), Oklahoma Central Cancer Registry (OCCR), and Vital Statistics from 1997 – 2009. Children without congenital anomalies were identified from a random sample of all births and matched on birth year with a ratio of 4:1 to children with anomalies. We then linked the databases, calculated descriptive statistics and assessed the relationship between congenital anomalies and childhood cancer using modified Poisson regression.

Ninety-one percent (91%) of those in the OBDR linked to birth certificates. Fifty-five percent (55%) of those in OCCR linked to the matched set of OBDR and random sample of birth certificates. We found that children with congenital anomalies had a 4.26 times higher risk of childhood cancer than children without congenital anomalies (95% CI: 3.14, 5.76).

Because this is the first linkage of this nature in Oklahoma, the process of working among different departments within the Oklahoma State Department of Health was important and innovative. This study provided an opportunity to work with the health department and contribute to the literature regarding the association between congenital anomalies and childhood cancer.

RADIATION INDUCED TNFα DEPENDENT SECOND SIGNALING FEEDBACK ASSOCIATED POST-TRANSLATIONAL NUCLEAR-IMPORT OF NFκB REGULATES TUMOR INVASION/METASTASIS IN HUMANN EUROBLASTOMA

Presenter: Faizan H. Khan

Faizan H. Khan, Satish Kumar Ramraj, Praveen Natt, Vijayabaskar Pandian, Natarajan Aravindan
Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Abtract: Ascertaining functional-specific orchestration of NFκB in response to IR may throw light on molecular blue print that underlies induced neuroblastoma (NB) relapse and metastasis. Accordingly, we investigated whether muting IR-triggered post-translational nuclear import of NFκB attenuates TNFα dependent second signaling feedback and attenuates IR-altered NB invasion and metastasis transcriptome. SH-SY5Y, IMR-32, SK-N-MC cells, exposed to 2Gy and allowed to incubate further for 1h or 24h, were treated with SN50. The cells were examined for NFκB DNA binding activity (EMSA), transactivation potential (QPCR) and intercellular secretion of TNFα (ELISA). IR triggered NFκB-TNFα transcriptional feedback was examined using luciferase reporter assay. Alterations in tumor invasion and metastasis transcriptome were assessed using QPCR profiling and selectively validated with immunoblotting. IR significantly induced NFκB DNA binding activity and this induction is completely and persistently (up to 72) suppressed both after blocking constitutive (1h) or post translational (24h) NFκB. Consistently, we observed a significant reduction in IR-induced transactivation and intercellular secretion of TNFα with both 1h and 24h post-IR SN50 treatment. Conversely, blocking TNF receptor resulted in sustained inhibition of NFκB but not AP-1 or SP-1. Luc promoter assay revealed a significant reduction in IR induced NFκB transcription after blocking TNF receptor. Blocking post-translational nuclear import of NFκB profoundly inhibited IR-induced tumor invasion and metastasis transcriptome (Table 1.). Immunoblotting for MMP2, PYK-2, SPA-1, Dnmt3b and Ask-1 validates the role of post-translational NFκB in IR regulated invasion/metastasis signaling. Together, these data demonstrates that IR induced second phase (post-translational) NFκB activation mediates TNFα-dependent second signaling and further implies that IR induced NFκB in cells that survive after treatment regulates tumor invasion and metastasis signaling.

TABLE 1

	SH-SY5Y	IMR-32	SK-N-MC
Total Genes	**95**	**95**	**95**
2Gy Up regulated	**63**	**42**	**71**
2Gy-1h SN50–1h attenuates	**63/63**	**37/42**	**65/71**
2Gy-1h SN50–3h attenuates	**62/63**	**37/42**	**71/71**
2Gy-24h SN50–1h attenuates	**59/63**	**35/42**	**71/71**
2Gy-24 SN50–3h attenuates	**63/63**	**37/42**	**71/71**
2Gy-1h SN50–1h/3h commonly attenuates	**62/63**	**34/42**	**65/71**
2Gy-24h SN50–1h/3h commonly attenuates	**59/63**	**32/42**	**71/71**
2Gy-1h/24 SN50–1h/3h commonly attenuates	**59/63**	**26/42**	**65/71**

POTENTIAL OF TURMERIC FRACTIONS IN MITIGATING THE ONSET OF ONCOGENESIS IN MOUSE MODEL OF RADIO-PROTECTION

Presenter: Faizan H. Khan

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Abtract: Ascertaining radiation-induced normal tissue damage and identifying a radio-protective "deliverable" have a momentous importance in the mitigation of environmental radiation injury, particularly against radiation-bioterrorism. Accordingly, we investigated the effect of crude, characterized fractions of turmeric and synthetic analogue of curcumin in the prevention of radiation-induced onset of oncogenesis using a mimic partially-immuno-compromised mouse model. Seven weeks old male heterozygous nude mice were either mock-irradiated, exposed to single acute (10Gy) dose of radiation with or without crude, characterized fractions (Oil Free Extract, Curcumin) of turmeric or its synthetic analogue (EF24) post-treatment. After the response period of 24h, gut tissues were examined for the modulations in 88 known oncogenes using real-time multiplex QPCR profiling. Modulations in VEGFA and TNFα were further validated with ELISA. Compared to mock-irradiated animals, exposure of acute radiation, profoundly upregulated 84 oncogenes in mouse gut. Conversely, pre-treatment with crude extract, oil free extract, curcumin or EF24 significantly inhibited 74, 82, 55 and 65 genes out of 84 radiation-induced oncogenes respectively. ELISA analysis validates the transcriptional expression and further confirms the translation of this radiation or drug response to the protein level. These data strongly suggests that crude turmeric, characterized fractions or its synthetic analogue may significantly target the radiation induced onset of oncogenes and thereby potentiate radioprotection. Further the data clearly implies that oil-free extract of turmeric is relatively more potent than other fractions and may serve as the "deliverable" in this setting.

IMPACT OF THE HISTONE DEMETHYLASE JMJD2A ON PROSTATE CANCER DEVELOPMENT

Presenter: Tae-Dong Kim, PhD

Tae-Dong Kim, Ralf Janknecht
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Abtract: 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 3. Although recent observations have shown oncogenic activity of JMJD2A, little is known about its role in prostate cancer progression.

In our study, we showed that JMJD2A expression was highly elevated in human prostate cancer compared with normal tissues. 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) in the prostates than the age-matched wild-type mice. A loss-of-function confirmed that JMJD2A promoted cell proliferation in LNCap prostate cancer cells. Furthermore, JMJD2A increased MMP1 expression through binding to proto-oncogene ETV1.

These findings suggest that JMJD2A functions as an oncogene and plays a critical role in prostate cancer development.

DEVELOPMENT AND EVALUATION OF A VASCULAR-TARGETED ENZYME PRODRUG THERAPY FOR BREAST CANCER

Presenter: John Krais

John Krais and Roger Harrison
Bioengineering Program and School of Chemical, Biological and Materials Engineering, University of Oklahoma

Introduction: The use of targeted therapeutics is a promising approach for the development of new cancer treatments that seek to reduce the devastating side effects caused by the systemic administration of current drugs. This study evaluates a fusion protein developed as an enzyme prodrug therapy targeted to tumor vasculature. Cytotoxicity is localized to the site of the tumor using a protein fusion of annexin V and bacterial purine nucleoside phosphorylase (PNP). Annexin V acts as the tumor targeting component of the fusion protein as it has been shown to bind to phosphatidylserine expressed externally only on cancer cells and the endothelial cells of tumor vasculature. The enzymatic component of the fusion, PNP, converts the FDA approved cancer therapeutic, fludarabine, into a more cytotoxic form. This conversion allows for increased impact at the site of the tumor, while decreasing side effects resulting from the high systemic concentration necessary for the current fludarabine-only treatments.

Methods: A fusion of Escherichia coli purine nucleoside phosphorylase and human annexin V was produced and purified in bacteria. 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 fluorescent microscopy. The same cell lines were used for a cytotoxicity analysis of the enzyme prodrug treatment. An in vivo study was conducted using SCID mice and an MDA-MB-231/GFP xenografts model that examined treatment efficacy and possible synergism with docetaxel, a chemotherapeutic shown to increase externalization of phosphatidylserine in vivo for endothelial cells in the tumor vasculature.

Results: Recombinant production and purification of the fusion protein has yielded an active protein and promising in vitro results. Our in vitro results show successful binding and killing of cancer and endothelial cells representative of tumor vasculature. Mild tumor growth suppression was achieved in vivo with the treatment. Docetaxel treatment groups showed strong inhibition of tumor growth; however the tolerated dose was not sustainable for the extent of the treatment.

Conclusions: The targeted enzyme prodrug therapy produced positive results with two breast cancer cell lines and endothelial cells, with minimal impact on normal endothelium. These results suggested that this treatment has a positive therapeutic potential with reduced side effects upon advancement to in vivo trials. Unfortunately, the success did not translate as expected to the in vivo study; however, initial indications of synergism with docetaxel suggest exciting possibilities for other phosphatidylserine-targeted enzyme prodrug strategies, upon optimization of docetaxel dose.

STRUCTURE ACTIVITY RELATIONSHIP STUDIES TO IMPROVE CANCER DRUGS

Presenter: Caitlin Kriewall, Wm. Preston Carroway, Kelsie Magiera

Caitlin Kriewall, Wm. Preston Carroway, Kelsie Magiera, Dallas New, Dana Rundle
Department of Chemistry, University of Central Oklahoma, Edmond, OK

Abstract: The objective of this study was to determine whether any of twenty-six E series heteroarotinoid compounds prepared by Dr. K. Darrell Berlin of Oklahoma State University were eligible for further research as cytotoxic agents toward ovarian cancer cells. The E series compounds are further structural optimizations to increase solubility while preserving the cytotoxic effect of the heteroarotinoid, SHetA2. The E series class of compounds and SHetA2 are known as flexible heteroarotinoids (FlexHets) due to increased structural flexibility gained by substituting the linker region of the molecule with a more flexible urea or thiourea linker. SHetA2 has a known 10 µM LC50 in ovarian cancer cell lines, but has no comparable effect on normal cells in culture. The cytotoxicity of the E series FlexHets was compared to that of SHetA2 utilizing the Promega™ Cell Proliferation Assay in cell culture models using A2780 and SK-OV-3 human ovarian cancer cell lines. Five E series compounds showed cytotoxicity comparable to that of SHetA2. An evaluation of structural features in E series compounds that promote cytotoxicity versus those features that do not will lead to the development of improved heteroarotinoids for possible therapeutic intervention. Currently the synthesis of E1 is underway to generate an amount sufficient for further analysis of its intracellular effects, and other potent E series compounds will be synthesized after successful synthesis and purification of E1. Further studies of E series compounds will be done by kinase assay, kinase inhibition, and Western blotting to examine which signaling pathways and proteins these heteroarotinoids act upon to induce cell death.

DIFFERENTIAL ROLES OF AUTOPHAGY IN OVARIAN CANCER AND HEALTHY CELLS IN RESPONSE TO SHETA2 DRUG

Presenter: Andrew Long

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

Abstract: SHetA2 is a small molecule flexible heteroarotinoid (Flex-Het) that differentially induces apoptosis in cancer, but not healthy cells. This study tested if autophagy modulates SHetA2 sensitivity in human ovarian cancer cell lines that exhibit greater- or reduced-SHetA2 sensitivity (A2780 or SK-OV-3, respectively) and in SHetA2-resistant human ovarian surface epithelium (HOSE) cells. SK-OV-3 exhibited higher basal and greater SHetA2-induced autophagy compared to A2780. HOSE elicited autophagy in response to rapamycin, but not SHetA2. Inhibition of autophagy with either 3-methyladenine (3-MA) or Beclin 1 siRNA enhanced SHetA2 cytotoxicity and caspase cleavage in SK-OV-3, but 3-MA had no effect in A2780 or HOSE. Conversely, induction of autophagy with rapamycin reduced SHetA2 cytotoxicity in SK-OV-3, and not in A2780. SHetA2 induced caspase 9 and 3 in both cancer lines, but induced caspase 8 in A2780 only. Caspase 3 cleavage was associated with Beclin 1 cleavage in both cancer lines, although with an earlier time course in A2780. Increasing cancer severity of human ovarian cancer histology in a tissue microarray (TMA) was significantly inversely associated with punctate LC3B staining, indicating basal levels of autophagic vesicles, and significantly directly associated with punctate cleaved caspase 3 staining, indicating basal levels of apoptosis. In summary, although reduced basal levels of autophagy and increased basal levels of apoptosis correlated with ovarian cancer progression, inducible autophagy interferes with SHetA2-apoptosis in a cancer cell line dependent manner, and not in healthy cells, suggesting that addition of an autophagy inhibitor could enhance SHetA2 therapy in a subset of ovarian cancer patients.

Health Beneficial Effects of Dietary Omega-3 Polyunsaturated Fatty Acids (n-3) on the Obesity-Associated Disease and Cancers Studied by Nutritional Proteomics

Presenter: Hiroyuki Matsumoto, PhD

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Abstract: Obesity raises risks of various types of cancers in esophagus, pancreas, colon and rectum, breast (after menopause), endometrium, liver, kidney, thyroid, gallbladder, and others. According to NHANES Study, total of 68.0% of adults at ages 20 and older are obese. Dietary supplement of fish oil rich in omega-3 polyunsaturated fatty acids (omega-3 PUFAs or n-3) is known to ameliorate obesity, promoting healthy living and longevity as reported in numerous nutritional and epidemiological studies. In contrast, consumption of meat rich in omega-6 (n-6) contributes to inflammatory disorders leading to metabolic syndrome, obesity, and cardiovascular diseases. Fish intake is positively associated with enhanced health and longevity according to numerous nutritional and epidemiological studies. In contrast, there are several meta-analysis studies of published data reporting the inconclusiveness on the dietary effect of n-3. The molecular mechanisms underlying in the health-beneficial dietary effect of fish oil on humans also remain unknown. We have been building an interdisciplinary effort on this campus to study the various aspects of dietary effects of n-3 and n-6 PUFAs using a mouse model with an intention to translate the knowledge into application to humans. Our strategy is, first, to establish a cohort of mice in which we can control pathological phenotypes such as obesity, metabolic syndrome and pre-diabetic conditions, non-alcoholic fat liver diseases, non-alcoholic steatohepatitis, and livers cancers, by manipulating the dietary ratio of n-3/n-6, and, second, to elucidate the underlying molecular mechanisms by proteomics and other biochemical approaches. In addition to these phenotypes in the obesity-associated disease axis, we also investigate other phenotypes that stem from the nutritional and life-style disturbances: this includes ageing, cognitive decline, and osteoarthritis. Two possible pathways exist that could explain the health beneficial effect of n-3; Pathway 1, n-3 such as EPA, DHA, and α-linolenic acid act as anti-inflammatory and neuroprotective agents, whereas n-6 such as arachidonic acid acts as proinflammatory by being converted into inflammatory eicosanoids. Especially, the neuroprotective agents generated *in vivo* include resolvins and (neuro)protectins that are converted from n-3 such as EPA or DHA. Pathway 2: GPR120, a G-protein-coupled receptor, has been identified as a membrane receptor specific to n-3, but non-responsive to n-6. Therefore, it is possible that the health beneficial effect of n-3 could be a series of signaling activation downstream of GPR120. These two pathways are not mutually exclusive; therefore, they can occur simultaneously. We discovered that enriched n-3 *in vivo* suppressed spontaneous occurrence of hepatocellular carcinoma compared to the mice with low n-3. Interestingly, we did not observe the suppressive effect of n-3 on breast cancer. The high n-3 altered expression of some proteins as detected by proteomics. Based on these we will discuss possible molecular mechanisms underlying the suppression of HCC by n-3. The interdisciplinary n-3 project is being conducted by collaborations within the following research groups at OUHSC; Dr. E. Anderson (DMEI), Dr. W. Sonntag (ROCA), Dr. S. Lightfoot (Pathology), Dr. T. Griffin (OMRF), Dr. D. Benbrook (Ob & Gyn), and Dr. M. Zou (Endocrinology and BMB).

Contribution of EMT in radiation resistance of breast cancer

Presenter: Meghna Mehta

Meghna Mehta, Yuhui Yuan, Huifeng Liu, Raymond E. Meyn, Rajagopal Ramesh, Anupama Munshi
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Abstract: Epithelial-Mesenchymal Transition (EMT) is a key developmental program that is often activated during cancer invasion and metastasis. EMT can be defined as a process that causes complete loss of epithelial traits such as E-cadherin expression and acquisition of mesenchymal properties, such as vimentin expression. EMT cells have stem cells properties and possess the characteristics of cell motility, invasiveness and chemotherapy resistance and these cancer stem cells may be responsible for mediating tumor metastasis and resistance to cancer treatments. However, very little is known about the role of EMT and cancer stem cells in modulating radiation response of human breast cancer cells. We compared expression levels of E-cadherin and other EMT related markers in ER-□ negative (MDA-MB-231 and Hs578t) and ER-□ positive (MCF-7) human breast cancer cells. Clonogenic cell survival assays showed that the cell lines expressing estrogen receptor (MCF-7) were more sensitive to increasing doses of radiation and had high expression of E-cadherin. In contrast, ER negative cells (MDA-MB-231 and Hs578t) had no detectable expression of E-cadherin and were more radioresistant. Clonogenic cell survival assays using MCF-M cells generated from the epithelial MCF-7 cells and expressing stable mesenchymal phenotype were more radioresistant compared to the parental MCF-7 cell line. We also transfected MDA-MB-231 and Hs578t cells with a CDH1-expression vector and isolated stable clones. These clones were selected and tested for radiosensitivity. MDA-MB-231 and Hs578t cells transfected with a control vector (pCMV) served as controls. Restoring E-cadherin expression radiosensitized the cells compared to the control vector cell line, suggesting that restoration of E-cadherin expression in mesenchymal-like cells produces a radiosensitizing effect. Our preliminary data demonstrates that EMT, detected as the loss of E-cadherin expression, may regulate tumor cell radiosensitivity, i.e. cells that have undergone EMT are relatively radioresistant compared to the lines that have retained the epithelial phenotype, which are relatively radiosensitive. Thus, there was a general correlation between EMT, based on loss of E-cadherin expression, and radioresistance. Overall, our results suggest that E-cadherin interacts with radiation and enhances the radioresponse of human breast cancer cells. Since it has been demonstrated that the process of EMT contributes to drug resistance and results in cells with CSC-like characteristics, we compared ALDH1 expression in ER positive (MCF-7) and ER negative (MDA-MB-231 and Hs578t) and transfected (MDA-MB231 CDH1 and Hs578t CDH1) cell lines. Our data shows that ALDH1 expression correlates with the ER status of the breast cancer cells, with a higher number of ALDH1+ cells in ER negative compared to ER positive cell lines. Also the transfected cell lines upon restoration of E-cadherin expression show a decrease in the ALDH1 + cell population. Our preliminary investigation leads us to believe that potentially resistant breast cancer stem cell populations appear to be overrepresented in ER negative breast cancer cell lines. Our observation concurs with clinical data that ER negative cancer are resistant to radiation therapy compared to ER positive breast cancers.

STRUCTURAL STUDIES OF HUMAN JMJD4 WITH X-RAY METHODS

Presenter: Blaine Mooers, PhD

Chiedza Kanyumbu, Irene Chen, Kyle Cahill, and Blaine Mooers
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Abstract: JMJD4 is a member of a large family of proteins (30 proteins identified so far) that are associated with the demethylation of the methyllysines in the exposed N-terminal tails of histones. Modification of these lysines changes chromatin structure and provides an additional layer of gene regulation that is important in the establishment and maintenance of cell identity and in diseases including several cancers. Lysine demethylation is carried out by demethylases from two families of proteins with the largest family being the Jumonji C (JMJC) histone demethylating enzymes. The JMJC family members are associated with several cancers. For example, in homozygous JMJD5 $^{-/-}$ knockout mice, the absence of JMJD5 leads to the upregulation of the tumor suppressor p53. JMJD5 is also upregulated in leukemias and breast cancer.

Recent crystal structures of three members of the Jumonji C family helped focus biochemical experiments by providing structure-based hypotheses. For example, the atomic resolution crystal structure of JMDJ5 called into question previous biochemical results that suggested it had lysine demethylase activity and led to improved experiments showing that it does not. Recent phylogenetic analyses by others show that JMJD4 is more similar to JMJD5 and JMJD6 than to the known lysine demethylases, so further experimental characterization of JMJD4 promises to reveal that JMJD4 has a function that is unique in the Jumonji C family. No structural work has been published on JMJD4. Our immediate objective is to obtain sufficient quantities of pure JMJD4 for structural studies in solution by small angle X-ray scattering and in crystals by X-ray diffraction. Towards this end, we have produced milligram quantities of recombinant protein and are determining critical biophysical properties of the protein to guide crystallization. Our central hypothesis is that the domains flanking the JMJC domain confer substrate specificity. JMJD4 shares the JMJC domain of known structure but has additional domains of unknown structure. To test the central hypothesis, we will determine the crystal structure of JMJD4 and compare the structures of the flanking domains to known protein structures.

PELITINIB REGULATES RADIATION-INDUCED p65-DEPENDANT TELOMERASE ACTIVATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

Presenter: Praveen Natt

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Abstract: Our earlier studies indicated that ionizing radiation (IR) induces NF-κB-dependent clonal expansion of therapy resistant tumor cells. Herein, we investigated whether mitigation of NF-κB-dependent telomerase activation by EGFR tyrosine kinase inhibitor can enhance IR-induced cell killing. SCC-4 and SCC-9 cells exposed to IR with or without Pelitinib were examined for NF-κB and hTERT transcription using luciferase reporter assays. NF-κB-dependent hTERT transcription was confirmed by either muting NF-κB or by using hTERT constructs lacking NF-κB binding sites. hTERT, mRNA, telomerase activity and cell survival of tumor cells were analyzed using QPCR, TRAP and clonogenic assay, respectively. Pelitinib inhibited IR-induced NFκB, telomerase activity and hTERT transactivation. Ionizing radiation-induced telomerase activity is regulated at the transcriptional level by triggering TERT promoter activation. Functional NF-κB mediates telomerase activity by binding to the κB binding region in the promoter region of TERT. Elimination of the NF-κB recognition site on telomerase or muting NF-κB compromises IR-induced telomerase promoter activation. We found that Pelitinib inhibited IR-induced TERT transcription, transactivation and telomerase activation in IR-exposed and NF-κB-overexpressed cells. Furthermore, Pelitinib potentiates IR-induced cell killing. Our results strongly suggest that IR-induced NFκB- mediated cell survival is supported by telomerase activation. We propose that if this pathway can be inhibited with Pelitinib treatment, one could further enhance therapeutic outcome in squamous cell carcinoma.

IRREVERSIBLE EGFR TYROSINE KINASE INHIBITOR, EKB-569 POTENTIATES RADIOTHERAPY IN TUMOR CELL KILLING

Presenter: Praveen Natt

Praveen Natt, Faizan H. Khan, Vijayabaskar Pandian, Satish Kumar Ramraj and Natarajan Aravindan
Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Abstract: EKB-569, an irreversible EGFR tyrosine kinase inhibitor has shown potential therapeutic efficiency in solid tumors. However, its synergistic/complementary cell-killing potential alongside radiotherapy, if any, and, underlying molecular orchestration remains to be explored. We investigated the effect of EKB-569 on radiation (IR) associated NFkB-dependent cell death. SCC-4 and SCC-9 cells exposed to IR (2Gy) with or without EKB-569 were analyzed for transactivation of 88 NFkB pathway molecules, NFkB DNA-binding activity, translation of NFkB downstream (Birc1, 2 and 5) molecules and cellular outcome including cytotoxicity and apoptosis. Selective targeting of IR-induced NFkB by EKB-569 and its influence in cell-fate was assessed by overexpressing (p50/p65) or silencing (DIkBα) NFkB. QPCR profiling revealed a significant induction of 74 NFkB signal transduction molecules after IR, of which, 72 were suppressed with EKB-569. EMSA revealed a dose-dependent inhibition of NFkB activity after EKB-569 treatment. More importantly, EKB-569 inhibited IR-induced NFkB in a dose-dependent manner and this inhibition remained consistent at least up to 72h. Immunoblotting revealed a significant suppression of IR-induced Birc1, 2 and 5 with EKB-569. We observed a dose-dependent inhibition of cell viability (examined by trypan blue method) increased cytotoxicity (assessed by MTT assay) and induction of apoptosis (Acridine orange staining) with EKB-569. Evidently, EKB-569 significantly conferred IR-inhibited cell viability and increased apoptosis. Blocking NFkB similarly augment IR-inhibited cell death. Conversely, NFkB overexpressed cells exhibit complete suppression of NFkB-dependent cell survival upon EKB-569 treatment. Together, these data clearly portraits that EKB-569 in combination with IR potentiates the therapeutic efficiency for squamous cell carcinoma and further delineates that EKB-569 associated radiosensitization may involve selectively targeting IR-induced NFkB-dependent survival signaling.

TARGETING LUNG TUMOR ANGIOGENESIS: TRANSLATIONAL POTENTIAL FOR LKB1 TUMOR SUPPRESSOR GENE

Presenter: Imoh Okon, PhD

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Introduction: Tumor angiogenesis and metastasis remain the leading causes of cancer-related mortality. Although anti-tumor properties of Liver Kinase B1 (LKB1) have been previously described in human neoplasm, a mechanistic link between LKB1 and tumor progression has yet to be fully explored. The prevalence of frequent LKB1 mutations in lung tumors (~30%) prompted investigation of its tumor suppressor functions in the disease. Here, we demonstrate the attenuation of tumor-promoting processes, including aberrant cell growth, angiogenesis and metastasis by LKB1 *in vitro* and *in vivo*.

Methods: Recombinant LKB1 protein or transient LKB1-vector was transfected into LKB1- deficient A549 lung cancer cells, while endogenous LKB1 expression was stably silenced in H1792, a stage IV, highly metastatic lung cancer cell line. Endogenous LKB1-expressing H1299 and H1703 lung cancer cell lines were also utilized. Angiogenesis was assessed by chorioallantoic membrane (CAM) assay which involved subcutaneous implantation of LKB1 null or positive cells into CAMs of 10-day old chick embryos, while tumor development and growth was investigated in nude mice. Cell proliferation and tumor metastasis, as a function of invasive and migratory potentials of LKB1-deficient or -expressing cancer cells was measured using the xCELLigence label-free, real-time system from Roche (Indianapolis, IN). Caspase-3 activity was determined by the EnzChek Caspase-3 Assay Kit #2 from Molecular Probes (Eugene, OR).

Results: LKB1-deficient A549 cells demonstrated strong angiogenic potential compared with LKB1-expressing H1299 or H1703 cell lines, as measured by vessel density in the CAM assay. Increased migration and invasion was also evident in A549 cells, indicative of a stronger metastatic potential compared with H1299 or H1703 cells. Ectopic gain-of-function experiments employing LKB1-expression vectors or recombinant LKB1 proteins correlated with decreased cell growth in A549 cells. Attenuation of AKT and caspase-3 signaling pathways contributed to the observed growth inhibition demonstrated by LKB1-expressing cells. Conversely, loss-of-function experiments utilizing stable LKB1 knock-down (shRNA) in H1792 cells correlated with tumor development and growth in nude mice, as well as increased angiogenesis in chick CAM assay. Enhanced migration and invasion was evident in LKB1-null cells compared with control (scramble shRNA) group.

Conclusion: LKB1-mediated repression of tumor growth, angiogenesis and metastasis was determined *in vitro* and *in vivo*. Recombinant LKB1 protein demonstrated strong anti-tumor growth properties suggesting potential development of an LKB1 mimetic for therapeutic applications. Furthermore, LKB1 or the loss of its expression could provide potential biomarker application in a subset of metastatic lung tumors. In addition to the regulation of AMPK-mTOR pathway, and NF-κB transcription factor, novel mechanistic insights of anti-tumor LKB1 functions is currently under investigation.

QUALITATIVE INTERVIEWS WITH SMOKERS FOLLOWING E-CIGARETTE SAMPLING

Presenter: Elisha R. Oliver, MS

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Abstract: The prevalence of e-cigarettes (ECs) use continues to increase, as more smokers are becoming aware of these products. Understanding smokers' perceptions of ECs following initial use and after viewing popular EC brand websites may have important implications not only for individual smoker's health but for public health policy. Eighteen participants (67% female, 78% White, M_{age}=40.1y, M_{cpd}=17.9, $M_{fagerstrom}$=5.06) completed a qualitative interview after sampling 3 different EC brands and their own brand cigarette (OBC). While sampling each EC, participants were allowed to view printed website screen-shots of the EC being sampled. An open-ended interview script was used for each participant. Interviews lasted approximately 45-60 minutes and were digitally recorded. Interview responses were analyzed for emerging themes which were both hand coded for inductive codes and using NVivo software. Codes were then categorized in a hierarchical system for use in a grounded theory approach. Overall themes included stress and stigma associated with tobacco use, motivations for cessation, and e-cigarette socio-economic and health perceptions. Stress and stigma: with the use of ECs, participants perceived intimate relationships would be improved by no longer having to mask the smell of smoke and professional opportunities would increase due to improved hygiene (smell of smoke on clothes, breath, and body). Motivation for cessation: participants expressed the belief that using ECs could help them quit smoking given that ECs reduced cravings significantly while also giving them an experience similar to smoking. Socioeconomic and health perceptions: noted large motivators of continued EC use were participants perception that EC use would likely lead to significant health benefits and cost savings over their OBC. Overall, this study indicates that just brief sampling and web-page viewing of 3 popular EC brands can lead to smokers perceiving the EC as having significant beneficial qualities affecting not only their health but their quality of life.

RADIATION-INDUCED MMP9 MAINTAINS REL SIGNALING THROUGH SECOND-SIGNALING FEEDBACK VIA BOTH ERK AND IKK ACTIVATION AND ENDORSES DELAYED INVASION AND METASTASIS OF NEUROBLASTOMA

Presenter: Vijayabaskar Pandian, PhD

Vijayabaskar Pandian, Ryan Major, Faizan H. Khan, Satish Kumar Ramraj, Praveen Natt, and Natarajan Aravindan
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Abstract: Tumor recurrences continue to remain high in neuroblastoma (NB), and a substantial fraction of those develop metastatic disease with only 10% survival in systemic recurrences. Efficient and improved therapeutic strategy can be developed through targeted drug delivery approach and by intervening molecular pathways operating in response to tumor recurrence. Herein, we investigated the onset and maintenance of metastatic signal transduction in neuroblastoma (SH-SY-5Y, MC-IXC, SK-PN-DW and IMR-32) cells that survive after radiotherapy. Gelatin zymography revealed that exposure to radiation induces significant and consistent increase in MMP2 and MMP9 activity. Further, muting radiation induced NFkB with dominant negative mutant IkB and/or forced expression of NFkB (p50/p65 sub-units) in these cells affirmed the influence of radiation-induced NFkB in MMP9 transactivation (QPCR), translation (immunoblotting) and activity (sequence specific substrate based high sensitive fluorogenic assay). Interestingly, blocking radiation-induced MMP9 with GM-6001 profoundly inhibited p65 transactivation and nuclear localization. More importantly, blocking radiation-induced MMP9 greatly introverted radiation-induced phosphorylation of IKK in these cells. Furthermore, radiation increased both transactivation and activity of ERK-1 (active ERK/phosphor-transferase immunoprecipitation) in neuroblastoma cells. This pathway was further defined (MMP9 blocking and activation, PMA studies) to show that radiation-induced functional MMP9 is necessary for activation of ERK- and NFkB-dependent onset of metastasis (tumor invasion and metastasis transcriptome profiling) in surviving NB cells. Selective MMP9-dependent ERK regulation was confirmed with futile inhibition of ERK activity in aprotinin treated cells. Together, these data strongly suggest that radiation induced NFkB-dependent MMP9 reinforces radiation-induced delayed invasion and metastasis. Further, these results imply that the MMP9 dependent reinforcement may involve dual signaling feedback activation of NFkB though ERK and IKK phosphorylation.

ANTI-OXIDANT RICH SEAWEED POLYPHENOLS TARGET MULTI-SIGNALING CASCADE AND ALLEVIATES PANCREATIC CANCER PROGRESSION

Presenter: Vijayabaskar Pandian, PhD

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Abstract: Pancreatic cancer (PC) remains the fourth leading cause of cancer death with an unacceptable survival that has remained relatively unchanged over the past 25 years. The presence of occult or clinical metastases at the time of diagnosis together with the lack of effective chemotherapies pose a dire need for designing new and targeted therapeutic deliverables that favors the clinical outcome. Herein, we investigated the anti-tumorigenic potential of polyphenols from five different brown-algae in human PC cells (MiaPaCa-2, Panc-1, BXPC-3 and Panc-3.27). Total anti-oxidant capacity (TAC) analysis on stepwise polyphenol separations with increasing polarity (Hexane-DCM-EA-methanol) identified high levels of TAC in DCM and EA extractions across all seaweeds assessed. All DCM and EA separated polyphenols induced a dose-dependent inhibition of cell proliferation. Further, these polyphenols profoundly inhibited cell viability (trypan blue exclusion) and enhanced DNA damage (acridine orange/Ethidium bromide staining and DNA fragmentation) in all the cell lines investigated. More importantly, luciferase reporter assay revealed a significant inhibition of NFκB in the cells treated with polyphenols. Interestingly, QPCR analysis identified a differential yet definite regulation of pro-tumorigenic EGFR, VEGFA, AKT, hTERT, kRas, Bcl2, FGFα and PDGFα transcription in cells treated with DCM and EA polyphenols. Immunoblotting validates the inhibitory potential of seaweed polyphenols in EGFR phosphorylation, kRas, AurKβ and Stat3. Together, these data suggest that intermediate polarity based fractions of seaweed polyphenols may significantly potentiate tumor cell killing and may serve as potential drug deliverable for PC cure. More studies dissecting out the active constituents in potent fractions, mechanisms of action and synergism, if any, are warranted and are currently in process.

IL-24 PHOSPHORYLATION IS CRITICAL IN REGULATING THE AKT-MTOR SIGNALING PATHWAY ASSOCIATED WITH CANCER SURVIVAL AND METASTASIS

Presenter: Janani Panneerselvam, PhD

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Purpose of the Study: Interleukin (IL)-24 is a novel cytokine/tumor suppressor gene that has demonstrated potent anticancer activity in preclinical and clinical studies. Studies have shown protein functions can be regulated by post-translational modifications (PTMs). Since the IL-24 DNA sequence indicates the presence of five phosphorylation sites and that phosphorylation is known to regulate the function of a protein, we investigated whether IL-24 phosphorylation is required for exhibiting its anticancer activities. In vitro molecular and cellular studies were conducted using a human lung cancer cell line as a model.

Experimental Procedure: Human H1299 lung tumor cell line was stably transfected with a tetracycline (Tet)-inducible plasmid vector carrying the IL-24-wild-type (IL-24wt) or –IL-24 with global knock-down of all five phosphorylation sites (IL-24mt) cDNA. Furthermore siAKT and myristoylated Akt (myrAkt) transfection studies were also performed. The functional importance of IL-24 phosphorylation and its Akt mediated effect were determined by assessing the Akt/mTOR signaling pathway and the consequence of its inhibition on cell viability, cell migration, and invasion.

Results: Expression of IL-24wt but not IL-24mt inhibited cell growth and reduced colony formation on soft-agar. Additionally, IL-24wt significantly suppressed the migration rate and invasion of tumor cells across matrigel compared to cells expressing IL-24mt. Reverse-phase protein array (RPPA) assay revealed differences in expression levels of Akt and its downstream targets between H1299 cells expressing IL-24wt and IL-24mt. Validation of RPPA data by Western blotting analysis demonstrated expression of phosphorylated (p)-AKT and its downstream targets such as p-GSK-3β, p-mTOR, p-FOXO1, p-YAP1, and Cyclin D1 were markedly reduced with an increased expression of p27 and p-beta-catenin in H1299 cells expressing IL-24wt compared to H1299 cells expressing IL-24mt. Studies involving siRNA-mediated knockdown of Akt or overexpression of myr-Akt protein confirmed IL-24wt but not IL-24mt mediated its anticancer activity through the Akt signaling pathway. Additionally, critical proteins involved in the mTOR signaling pathway were also significantly suppressed in H1299 cells expressing IL-24wt but not IL-24mt. Finally, micro (mi) RNA array analysis revealed IL-24wt regulated the expression of oncomiRs.

Conclusion: Our results demonstrate for the first time, phosphorylation of IL-24 is functionally important and required for mediating its anticancer activities via inhibiting the Akt/mTOR pathway. Additional molecular studies are underway to identify the specific phosphorylation site (s) required for the IL-24-mediated anticancer activities.

TARGETED ENZYME PRODRUG THERAPY FOR METASTATIC PROSTATE CANCER – A COMPARATIVE STUDY OF THREE FUSION PROTEINS

Presenter: Katrin Passlack

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Abstract: Prostate cancer (PC) is the most common non-skin malignancy and the second leading cause of cancer-related death in American men, yet remains essentially incurable. Our objective is to develop a targeted, non-viral, enzyme/prodrug therapy to treat metastatic PC with minimal side effects. To achieve this, we have designed three novel fusion proteins (FP) each consisting of human annexin V (AV) and an enzyme without human homologs, thereby avoiding activation in healthy tissues. AV serves as the targeting arm via a high affinity to phosphatidylserine (PS), 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 vasculature. PS expression was increased prior to FP treatment via low dose (50 pM) docetaxel treatment. The FP enzymes are: (i) purine nucleoside phosphorylase (PNP) – converts fludarabine (FD) into 2-fluoroadenine (2-FA), (ii) L-methioninease (MT) – converts methionine (Met) to methanethiol and selenomethionine (SeMet) to methylselenol, and (iii) cytosine deaminase (CD) – converts 5-fluorocytosine (5-FC) to 5-fluorouracil. Binding strength of FPs to PS and cytotoxicity of all three systems were evaluated for human PC-3 prostate cancer cells.

Binding of all FPs to PC-3 cells was found to be relatively strong with Kd ranging from ¬0.06-0.6 nM. PNP-AV/FD produced 80% cell death at concentrations as low as 5 µM and was as effective as 2-FA, whereas FD treatment alone caused minimal cytotoxicity at concentrations up to 10 µM. MT-AV/SeMet treatment produced 90% cell death at SeMet concentrations of 500 µM after 3 days, whereas SeMet alone was not cytotoxic until 1000 uM concentrations. CD-AV/5-FC treatment produced only 60% cytotoxicity at concentrations of 5000 µM 5-FC in 9 days. Docetaxel treatment showed a significant increase in killing velocity and efficacy for the PNP-AV/FD and CD-AV/5-FC systems. The three novel FP/prodrug systems show promise for the targeted treatment of PC with minimal side effects. Future directions will consist of in vivo studies and studies with PEGylated FPs.

DESCRIPTIVE EPIDEMIOLOGY OF MALIGNANT MELANOMA IN OKLAHOMA 2000-2010

Presenter: Anne Pate, PhD

[1]Carol Strongin, MPH, [2]Anne Pate, PhD, [2]Amber Sheikh, MPH, [1]Janis Campbell, PhD
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Background: Oklahoma ranked 38th in incidence and 6th in mortality in the nation in 2008 for malignant melanoma. The Oklahoma Comprehensive Cancer Network (OCCN) has determined that melanoma is a priority issue in Oklahoma. This study was done because there are no other known descriptive epidemiology studies focused on malignant melanoma in Oklahoma.

Methods: Incidence, mortality, and staging were assessed to describe malignant melanoma in Oklahoma. This assessment initially reviewed incidence between 1997 and 2008. This previous analysis will be updated by using more current data for diagnosis years 2000-2010. Cancer incidence data from the Oklahoma State Department of Health (OSDH), Oklahoma Central Cancer Registry (OCCR) for diagnosis years 2000 through 2010 and mortality data from the OSDH, Health Care Information (HCI) for date of death 2000 through 2009 were used in the analysis. Age-adjusted incidence and mortality rates by race and gender were calculated as well as stage at diagnosis by race. Incidence rates at the county level were mapped using ArcGIS software. The relationship between race, income, and occupation was assessed against melanoma incidence using linear regression modeling.

Results: Age-adjusted incidence rates increased between 2000 and 2010 with males having higher rates overall. Mortality rates remained fairly stable over the time period with males having higher rates overall. Whites had higher incidence and mortality and a higher percentage of localized tumors at diagnosis than other races. GIS mapping displayed regional differences as the incident rates being fairly low in the southeastern counties. Whereas, moving westward, the incident rates increased and appear to be highest in the furthest western counties. Farming occupation was significantly associated with incidence rate (p=0.0038) for the years 1997-2008. Additional analysis will be conducted to assess if this association remains significant with an additional two years of data.

Conclusions: This study provides meaningful insights for malignant melanoma in Oklahoma. The findings agree with current literature that melanoma incidence is increasing in Whites and more in males than females, and that melanoma mortality is higher in males than females, and that most diagnosed tumors were of the localized stage. Within Oklahoma, this study shows that melanoma is associated with increasing outdoor sun exposure (farming occupation).

SEED MEDIATED SYNTHESIS OF DENDRITIC GOLD NANOPARTICLES WITH EFFICIENT PHOTOTHERMAL CANCER CELL KILLING AND CATALYTIC PROPERTIES

Presenter: Penghe Qiu, PhD

Penghe Qiu and Chuanbin Mao
Department of Chemistry and Biochemistry, University of Oklahoma

Abstract: We report our work on synthesizing AuNDs through a seed-mediated process in an ethanolic solution of hexadecylamine. In this synthetic system, the nanoparticles can be obtained very uniformly and their size can be manipulated facilely, in a single pot, by varying the amount of seeds but keeping all other precursors constant. The dendritic structure can be generated on gold seeds of different shapes, including, as demonstrated in this work, spherical, rod-like and triangular planar nanoparticles. Based on their near infrared (NIR) absorption, we demonstrated that these AuNDs are capable of killing cancer cells through the photothermal effect. Besides, we also investigated the catalytic performance of as-prepared AuNDs. We discovered that the AuNDs are at least 10 times more active than solid nanospheres composed of the same number of gold atoms.

TUMOR-HOMING NANOPARTICLES FOR TARGETED BREAST CANCER IMAGING AND TREATMENT

Presenter: Xuewei Qu

Xuewei Qu, William Thomas, Penghe Qiu and Chuanbin Mao
Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK, USA

Abstract: The photothermal gold nanorods (AuNRs) are expected to be used as a novel tumor-killing agent but the distribution of the isolated AuNRs cannot be controlled. To develop the aggregation of AuNRs in the tumors, we successfully identify a series of MCF-7 tumor-recognized peptides with a length of 15 residues by *in vivo* phage display, which is a convenient way to select peptides targeting cells or organs on the basis of very wide varieties of a phage library. After modifying the tumor-recognized peptide on the surface of AuNRs, the distribution of gold at the tumor position is increased by almost two times. The significant increase in tumor-binding efficiency makes the peptide-conjugated AuNRs very promising in photothermal therapy of cancers.

1. **Identification of tumor-targeting peptides by in vivo phage display**: 12 associated peptides were selected within 5 rounds of In vivo phage display. In all the 12 associated peptides, the sequence of AREYGTRFSLIGGYR, PKAFQYGGRAVGGLW, PVRYGFSGPRLAELW, RNVPPIFKEVYWIAQ and RTLIRMGTGAHAFAV those show the highest frequency in 5 rounds of selection are considered to be possibly tumor-specific.

2. **Evaluation of the tumor-targeting capability of the selected peptides by in vivo fluorescence imaging:** We first used the in vivo fluorescence imaging to study the accumulation of the selected peptides at the tumor sites. In the experiment, the synthesized peptides were labeled with Cy5 fluorescent tags at the C-terminal by biotin-streptavidin interaction. The significant fluorescence accumulation of the peptide PKAFQYGGRAVGGLW (figure. 1) showed was observed on the tumor site after five hours through in vivo circulation. These results suggest that the peptide obtained from the in vivo phage display is indeed highly efficient in targeting tumors.
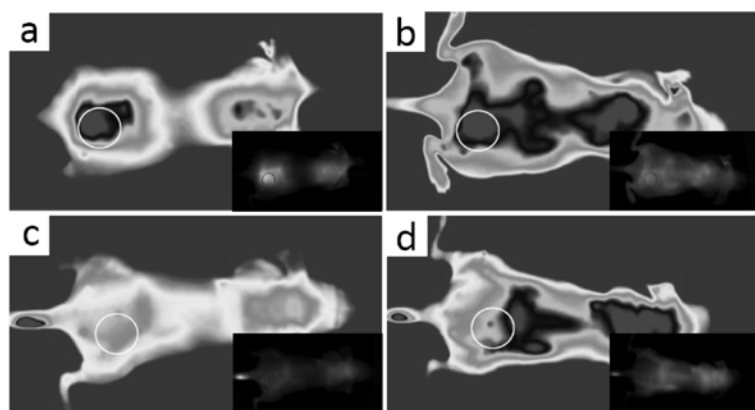
Figure 1. Nude mice injected with: fluorescence-peptide conjugates (a, b); fluorescence -streptavidin (c, d). Time: (a, c) 1 h after injection; (b, d) 5 h after injection.

3. **Quantitative study of in vivo distribution of peptide-conjugated AuNRs by the Inductively Coupled Plasma Mass Spectrometry (ICP-MS):** for quantitative study of the in vivo distribution, 1mg of the peptide-conjugated AuNRs or PEG stabilized AuNRs as controls were injected intravenously into the tumor-bearing nude mice. After 24 h in vivo circulation, the amount of gold in tumors and other organs

were quantified by the ICP-MS. The ICP-MS measurement showed that the concentration of the peptide conjugated AuNRs is almost twice as high as that of the PEG stabilized AuNRs (figure. 2). Also with the conjugation of tumor-targeting peptide, the non-specific retention of AuNRs in other organs has been significantly reduced. With the significant increase of affinity binding between the AuNRs and tumors, the peptide-AuNRs conjugates are expected to enhance the specific tumor-killing ability base on the current photothermal therapy of breast cancers.
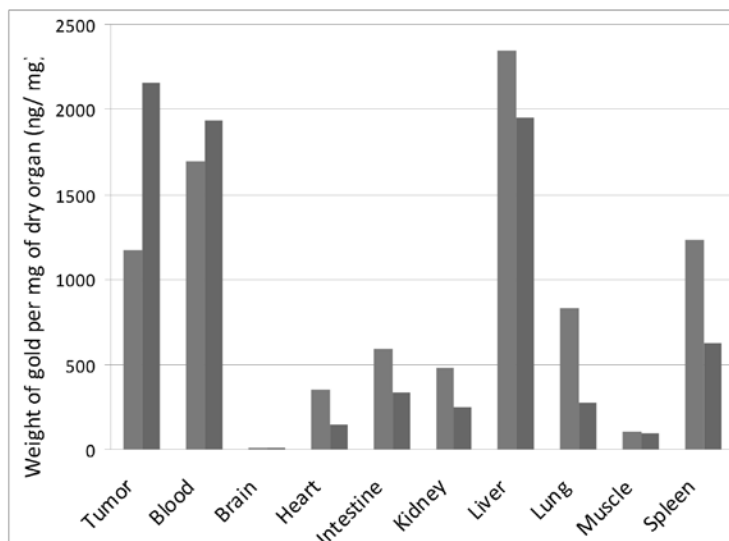

Figure 2. Blue: Control by PEG stabilized AuNRs; Red: AuNRs conjugated with tumor-targeting peptides.

HIGH SENSITIVITY DNA DAMAGE DETECTION ASSAY: POTENTIAL TOOL TO PREDICT CANCER RISK AND RESPONSE TO TREATMENT

Presenter: Lurdes Queimado, MD, PhD

[1]Wilbur Mills, [1]Elangovan Thavathiru, [1]Vengatesh Ganapathy, [1]Dini Chissoe, [1]Leslie Chandler, [3]Antonio Reis, [1,2,4,5,6]Lurdes Queimado

Departments of [1]Otorhinolaryngology, [3]Dermatology, [4]Cell Biology and [5]Pediatrics; [2]The Oklahoma Tobacco Research Center and [6]The Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA.

Background: Head and neck squamous cell carcinoma represents the sixth most common malignancy worldwide and is associated with great morbidity and mortality. Importantly, eighty-five percent of head and neck cancers are linked to tobacco use, and therefore are preventable. Still, many smokers are unable or unwilling to quit smoking. Carcinogens in tobacco smoke damage genomic DNA, causing frequent and specific patterns of mutations that initiate several types of cancer, including head and neck cancer.

The individual DNA repair efficiency of tobacco-induced DNA damage is expected to modulate the susceptibility to tobacco-induced cancer. However, technical limitations have hampered the measurement of in vivo tobacco-induced DNA damage and no predictable biomarkers of cancer risk have been identified. We developed a novel technique known as primer-anchored DNA damage detection assay (PADDA) to reliably detect DNA damage. PADDA is the first and only assay capable of accurately mapping (f-PADDA) and quantifying (q-PADDA) nucleotide and strand specific endogenous DNA damage and has higher sensitivity than other available assays to detect DNA damage caused by exogenous agents.

Aims: (1) To define the levels of persistent DNA damage in the oral mucosa of smokers and non-smokers. (2) To determine if persistent nucleotide damage at p53 co-localizes with tobacco-induced cancer mutational hotspots.

Methods: PADDA was used to determine the extent of tobacco-induced DNA damage in the oral mucosa of smokers and non-smokers. DNA damage was mapped and quantified on the p53 transcribed and non-transcribed strands of oral epithelial cells collected by oral scrapings. The location of p53 nucleotide damage was compared with reported tobacco-induced p53 mutational hotspots. Saliva cotinine levels were determined to confirm smoking status. Data were analyzed by chi-square goodness of fit and exact non-parametric tests.

Results: Our data show a significantly higher level of DNA damage in smokers than in non-smokers, and a difference in levels of DNA damage between DNA strands. Moreover, damage in the oral mucosa of smokers appears to have significantly higher mutagenic potential and to persist mainly at p53 nucleotides that are hotspots for mutation in tobacco-induced cancers.

Conclusion: Our study shows PADDA's ability to measure the extent of in vivo tobacco-induced DNA damage and repair in human cells, and reinforces the importance of smoking cessation. Of major clinical importance, our data show that tobacco-induced DNA damage persists preferentially in p53 nucleotides that are hotspots for mutation. PADDA's unprecedented ability to map sites of in vivo endogenous and induced DNA damage before mutation fixation as well as to quantify strand specific damage may become a critical tool for assessing cancer risk, prevention strategies, and tumor prognosis.

ACTIVATABLE PHOTOSENSITIZERS FOR MITOCHONDRIAL TARGETING AND PHOTODYNAMIC THERAPY

Presenter: Pallavi Rajaputra

Pallavi Rajaputra, Gregory Nkepgang, Ryan Watley, Youngjae You
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Abstract: This study focuses on synthesis and in vitro photodynamic activity of a laser activatable cationic photosensitizers targeting mitochondria to eventually minimize the side effects in cancer treatment. Mitochondria-specific photosensitizers were designed by taking advantage of the preferential localization of delocalized lipophilic cations (DLCs) in mitochondria. Three conjugates, CMP-Rh, CMP-tPP, and CMP-$(tPP)_2$, were successfully synthesized by linking the hydroxy core modified porphyrins (CMP-OH and CMP-$(OH)_2$) to either rhodamine B (Rh B) or one or two triphenyl phosphine (tPP) cations respectively via a saturated hydrocarbon linker. Their ability for delivering photosensitizers to mitochondria was evaluated using dual staining fluorescence microscopy and staining pattern was compared with a mitochondrial specific probe. Fluorescence imaging study suggested that CMP-Rh specifically localized in mitochondria. On the other hand, CMP-tPP and CMP-$(tPP)_2$ showed less significant mitochondrial localization. The conjugation of CMP to Rh and tPP did greatly improve intracellular uptake and in vitro photodynamic activity compared to CMP-OH. In addition, to evaluate the efficiency of the conjugates as photosensitizers, their photophysical properties and in vitro biological activities were studied in comparison to those of CMP-OH. All conjugates were capable of generating singlet oxygen at rates comparable to CMP-OH. This improved photodynamic activity might be primarily due to an enhanced cellular uptake. Our goal was to deliver CMP to mitochondria by conjugating it with DLCs (Rh or tPP). Rh moiety seemed an excellent delivery vector for CMP to mitochondria.

DIET DERIVED POLYPHENOL TARGETS EMT AND PLURIPOTENCY MAINTENANCE TRANSCRIPTOME IN PANCREATIC CANCER STEM CELLS

Presenter: Satish Ramraj

Satish Kumar Ramraj, Vijayabaskar Pandian, Faizan H. Khan, Praveen Natt, Natarajan Aravindan
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Abstract: Ascertaining the potentials of diet-derived phenolics in eradicating cancer stem cells (CSCs), that proliferate and self-renew extensively leading to the initiation and progression of tumor, may escort significant clinical implications. Recently, we have shown that black raspberry extract (RSE) potentiates pancreatic cancer (PC) cell killing by targeting transcriptional machinery. Herein, we investigated ex vivo the effect of RSE on the regulation of EMT, pluripotency maintaining and other stem cell related molecules in PC-CSCs. CD133+CD44+CD24+ESA+ PC-CSCs isolated from human PC xenografts developed in athymic NCr-nu/nu nude mice with human MiaPaCa2, BXPC3, Panc-1 or Panc-3.27 cells were maintained in vitro. PC-CSCs exposed to RSE (2.0µg) for 3h were assessed for transcriptional regulation of 93 stem cell related molecules using QPCR profiling. Expression and cellular localization of epithelial-to-mesenchymal transition (EMT) markers and pluripotent maintaining factors including ABCG2, E-Cadherin, N-Cadherin, MYB, MYC, Nanog and SOX2 in MiaPaCa2, BXPC3 xenografts were assessed using immunohistochemistry (IHC). The results revealed that RSE significantly inhibited 83, 50 and 54 stem cell related molecules in PC-CSCs isolated from xenografts developed using MiaPaCa2, Panc-1 and Panc 3.27 respectively. Of these, 27 genes were commonly suppressed by RSE in all three PC-CSCs population. Further, IHC staining showed complete repression of EMT and pluripotent markers in both MiaPaCa2 and BXPC3 xenografts. Together, these data imply that RSE may exert selective inhibition of EMT and pancreatic CSCs' self-renewal capacity and, may thus serve as a potential "deliverable" to negate PC initiation and progression.

ANTI-METASTATIC POTENTIAL OF SULFATED POLYSACCHARIDES FROM TURBINARIA CONOIDES IN PANCREATIC CANCER

Presenter: Satish Ramraj

[1,2]Caroline R Delma, [1]Satish Kumar Ramrajm, [2]Somasundaram S. Thirugnanasambandan, [1,2,3]Sheeja Aravindan, [1,5,6]Natarajan Aravindan
Departments of [1]Radiation Oncology, [5]Pathology and [6]Anesthesiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, [2]Center of Advanced Study in Marine Biology, Annamalai University, Parangipettai, TN, INDIA, [3]Peggy and Charles Stephenson Cancer Center, Oklahoma City, OK, USA

Abstract: Pancreatic cancer is one of the most deadly cancers with a five year survival rate of less than six percent. The poor prognosis can be attributed to the fact that more than three fourth of the patients have metastasis at the time of diagnosis. In view of the increasing evidence that sulfated polysaccharides attenuate tumor invasion, we attempted to evaluate the anti-metastatic potential of sulfated polysaccharide fractions from a marine brown alga, Turbinaria conoides in pancreatic cancer. Exposure of human pancreatic adenocarcinoma cells (MiaPaCa-2, Panc-1, BxPC-3 and Panc-3.27) to partially purified polysaccharide fractions showed a negative regulation of both the transcriptional activation (QPCR) and cellular expression (immunoblotting) of adhesion molecules, Mucin-16, E-Selectin and metastasis efficiency modifying SPA 1 and Dnmt3b. All encompassed, transcriptional profiling pertaining to tumor invasion and metastasis (QPCR profiling) revealed cell-type unique, yet comprehensive inhibition, including 62, 65, 64 and 51 of 93 transcripts in Mia PaCa-2, Panc-1, BxPC3 and Panc-3.27 cells, respectively. Extracellular matrix metalloproteinases MMP-2 and MMP-9, which play a significant and definite role in the invasion and metastasis of pancreatic cancer were completely muted as evidenced by reduced activity (by gelatin zymography) and secretion (by immunoblotting) in cells exposed to all fractions. Relatively, fraction V showed robust inhibitory potential in this setting. Together, these data suggest that fractions of sulfated polysaccharides, specifically fraction V, may serve as a potential drug deliverable to alleviate pancreatic cancer metastasis. This study prompts us to investigate further the active constituents in the sulfated polysaccharide fraction and their target binding affinity, (here in this case, to MUC16 and/or MMPs) and their mode of signal transduction.   These in vitro studies and studies testing its efficacy in an in vivo setting are currently in process in our laboratory.

SELECTIVE TARGETING AND TREATMENT OF PANCREATIC CANCER VIA THREE FUSION PROTEIN/PRODRUG COMPLEXES PLUS DOCETAXEL

Presenter: Antonietta Restuccia

[1]Antonietta Restuccia, [1]Katrin Passlack, [2]Carla Kurkjian, and [1]Roger Harrison1
[1]Bioengineering Program and School of Chemical, Biological and Materials Engineering, University of Oklahoma, [2]Hematology/Oncology Section, University of Oklahoma Health Sciences Center

Abstract: 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 treatment. We have developed three novel fusion protein (FP)/prodrug therapies to selectively target and kill pancreatic tumors and their metastases. The FPs are enzymes with nonhuman fused to a targeting arm of human annexin V (AV). AV binds to phosphatidylserine (PS), an anionic phospholipid component tightly segregated to the internal side of the plasma membrane in healthy cells but expressed on the external surface of tumor cells and vasculature. To increase PS exposure and AV binding sites, the cancer cells were treated with a subtoxic dose (200pM) of docetaxel. The FP enzymes are: (i) purine nucleoside phosphorylase (PNP) – converts fludarabine (FD) into 2-fluoroadenine (2-FA), (ii) L-methioninease (MT) – converts methionine (Met) to methanethiol and selenomethionine (SeMet) to methylselenol, and (iii) cytosine deaminase (CD) – converts 5-fluorocytosine (5-FC) to 5-fluorouracil. The binding strength of FPs to PS and cytotoxicity of all three systems were evaluated on human PANC-1 pancreatic cancer cells.

Binding of FPs to PANC-1 cells was relatively strong with K_d ranging from 0.01-0.8 nM. PNP-AV/FD treatment was as effective as 2-FA, killing 90% of the cells at a concentration of only 3 µM FD, while cells treated with FD alone maintained >100% viability after 6 days up to 20 µM FD. With Met augmentation, MT-AV/SeMet treatment produced 90% cell death at a concentration of 500 µM when the cells were pretreated with docetaxel, but in the absence of docetaxel, a 90% cell death was not obtained until much higher concentrations (5000 µM), indicating a significant effect of docetaxel on treatment efficacy. SeMet alone was not cytotoxic until 1000 µM concentrations. CD-AV/5-FC treatment produced 70% cell death at concentrations of 2000 µM, whereas 5-FC alone showed no toxic effects at concentrations as high as 10,000 µM over 6 days. We concluded that all three novel FP/prodrug systems show promise for the targeted treatment of pancreatic cancer with minimal side effects. Current work seeks to test the efficacy of these FP/prodrug systems on BxPC-3 and Capan-1 pancreatic cells with imminent future translation into *in vivo* work.

ROLE OF TICRR IN DNA REPLICATION

Presenter: Courtney G. Sansam, PhD

Courtney G. Sansam, Duane Goins and Christopher L. Sansam
Department of Cell Cycle and Cancer Biology, Oklahoma Medical Research Foundation

Abstract: The eukaryotic genome is replicated by the concerted activity of hundreds of bidirectional replication forks. The activation of these forks at sites called replication origins occurs throughout S-phase. The rate limiting and regulated step in the initiation of replication is the assembly and activation of the helicase. The activation of the helicase requires the DDK kinase (Cdc7+Dbf4) and S-phase CDK (CDK2). Studies in budding yeast have shown that the two essential CDK targets for DNA replication initiation are *Sld2* and *Sld3*. Phosphorylation of these proteins allow interaction with Dpb11 (TopBP1), a protein with essential roles in DNA replication and DNA damage signaling. Although no direct orthologs of *Sld2* and *Sld3* have been identified in mammalian cells, we discovered a novel gene, TICRR that plays a critical role in the regulation of DNA replication initiation that is a candidate *Sld3* ortholog. Phosphorylation of Ticrr by S-CDK is essential for both its physical association with TopBP1 and the initiation of replication in mammalian cells. Zebrafish embryos lacking the TICRR gene die during development. Our goal is to understand how deregulation of the TICRR-TopBP1 interaction affects the timing of S-phase entry, the length of S-phase, the order and timing of origin firing, genomic stability, and embryonic development.

AMPKα1 DEFICIENCY INCREASES DNA DAMAGE AND GENOMIC INSTABILITY

Presenter: Ping Song, PhD

Yanhong Zhou, Hairong Xu, Kathleen A Coughlan, Jie Chen, Ye Ding, Shaobin Wang, Ming-Hui Zou, Ping Song
Section of Molecular Medicine, Department of Internal Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, 73104

Abstract: Increasing evidence suggests that activation of adenosine monophosphate-activated protein kinase (AMPK), an energy gauge and redox sensor, causes cell cycle arrest and cell growth inhibition. Metformin, a well characterized AMPK activator and one of the mostly used anti-diabetic drugs, is reported to lower the incidence of cancers in human. However, the molecular mechanisms by which AMPK reduces cancer and/or suppresses tumor growth remain elusive. The aim of this study was to determine if AMPK lowers cancer by maintaining genome stability. The markers of DNA damage, cell cycle proteins, and aneuploids were monitored in cultured mouse embryonic fibroblasts (MEFs) isolated from wild type (WT, C57BL/6J), and general either AMPKα2 or AMPKα1 homozygous deficient (AMPKα2$^{-/-}$, AMPKα1$^{-/-}$) mice by western blots and flow cytometry. Deletion of AMPKα1 but not AMPKα2 in immortalized MEFs (iMEFs) significantly increased the levels of γH2AX-Ser139, p53 phosphorylation at Ser15 and total p53 protein levels. The phosphorylation of checkpoint kinase 1 (Chk1) at Ser345, a key indicator of DNA damage in immortalized MEFs, was also markedly elevated in AMPKα1$^{-/-}$ MEFs. Comet assay also confirmed DNA damage occurred in AMPKα1$^{-/-}$ MEFs. In AMPKα1$^{-/-}$ MEFs, histone acetylation including ac-H2A-K5, ac-H3-K9, ac-H3-K56, and ac-H4-K8 was dramatically elevated whereas centromere-specific binding proteins C (CENP-C) amount was markedly decreased. In addition, AMPKα1 deletion conferred an impaired centrosome in iMEFs and results in abnormal nucleus. Consistently, AMPKα1 deficiency triggered aneuploid (34%-66%). Finally, AMPKα1, not AMPKα2 deficiency conferred an anchorage-independent growth associated with colony formation in cultured iMEFs and the tumorigenesis in nude mice. Taken together, our results suggest that the deficiency of AMPKα1 rather than AMPKα2 instigates DNA damage and genomic instability, all of which may contribute to tumorigenesis.

ROLES OF HEAT SHOCK PROTEIN 9 AND BCL-2 IN THE MECHANISM OF SHETA2 INHIBITION OF RAT MAMMARY TUMORS

Presenter: Elangovan Thavathiru

[1]Elangovan Thavathiru, [2]Stan Lightfoot, [3]Daniel Zhao, and [1]Doris M Benbrook
[1]Department of Obstetrics and Gynecology, [2]Department of Pathology, [3]Department of Biostatistics and Epidemiology, OUHSC, Oklahoma City

Abstract: The small molecules, flexible heteroarotinoids (Flex-Het), induce differentiation, apoptosis and growth inhibition on ovarian cancer cells without harming normal cells. The lead Flex-Het, SHetA2 has completed preclinical development and exhibited in vivo cancer prevention activity with no signs of toxicity. The mechanisms by which this molecule induces apoptosis in ovarian cancer cells include its direct effects on mitochondria and the Bcl-2 family proteins. Recently, heat shock protein A 9 (HSPA9) was identified as a SHetA2 binding protein. In the present study, we attempted to determine if HSPA9 and Bcl-2 were involved in the activity of SHetA2 in a carcinogen MNU (N-Methyl N-Nitrosourea)-induced rat mammary tumor model and in the human triple negative breast cancer cell line (MDA-MB-231). In the animal model, two different doses of SHetA2 (low dose, 25 mg/Kg/day and high dose, 50 mg/Kg/day) were compared to a control diet lacking SHetA2 in groups of 15 rats each. The results demonstrated that the high dose of SHetA2 inhibited mitoses in tumor cells and inhibited tumor growth rate significantly as compared to the control group. Western blot analysis demonstrated reduced levels of Bcl-2 in tumors that arose in the SHetA2-treated groups in comparison to the control group. Furthermore, we are able to culture mammary tumor cells from MNU-induced mammary tumors that had developed in rats being fed with control and high dose SHetA2-containing diets. Cytotoxicity studies showed that the cells from control animals were more susceptible to SHetA2 than the cells from SHetA2-treated animals. Interestingly, Western blot analyses indicated elevated levels of Bcl-2 in the SHetA2-resistant rat tumor cells. In the human MDA-MB-231 cells, SHetA2 induced apoptosis in association with disruption of HSPA9 binding to its client proteins, p66shc and p53. Because p66shc and p53 are known to inhibit Bcl-2 and induce apoptosis when released from HSPA9, disruption of HSPA9 with these proteins is a logical initiation of the mechanism of SHetA2 induced apoptosis. Current studies are focused on validating the roles of these molecular events in SHetA2 apoptosis. In conclusion, SHetA2 induces similar effects on breast cancer cells as has been shown for ovarian cancer cells, and inhibition of HSPA9 is implicated in the initiating events in the mechanism of action.

Cancer Tissue Pathology Core

Description: 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 SCC members and other investigators.

Core services include:

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

PROMOTING REGULAR SCREENING MAMMOGRAPHY IN AN AMERICAN INDIAN COMMUNITY IN OKLAHOMA

Presenter: Eleni Tolma, PhD

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Introduction: American Indian/Alaska Native (AI/AN) women are less likely than white women to have received a mammogram within the past 2 years. A currently funded 3-year study is a continuation of a series of preliminary studies that have taken place at a tribal clinic in Oklahoma since 2005. We hypothesize that a sustained multi-component (clinical and community) intervention based on a sound theoretical model will yield improved rates of mammography uptake and clinical outcomes.

Methods: A Community Steering Committee representing the clinic, the tribal government and community members was formed. The priority population consists of healthy AI women without a history of breast cancer between the ages of 40-65. The study has three aims: 1) Conduct a needs and resource assessment of the priority population through focus groups, key informant interviews and quantitative data analysis based on the administration of the Women's Health Survey, b) Utilize the needs and resource assessment data to refine the overarching intervention Logic Model and develop a community-driven intervention program, and c) Pilot-test the intervention, and upon the completion of the pilot, refine the proposed intervention and conduct an evaluation of the intervention by using a quasi-experimental evaluation design. The study utilizes a Community Based Participatory Research approach.

Results: We have just completed aim 1, and have partially completed aim 2. The results of the formative research (aim 1) indicated that: a) AI women still lack knowledge of mammograms, b) The inconsistency of mammogram guidelines add to this lack of knowledge, c) Many AI women felt that a holistic approach to their health is preferable, d) Physicians are the most influential individuals to women and therefore, communication between physician and patient should include an open dialog on mammograms, e) Social modeling is an important motivating factor and participants suggested that the Native community as a whole can encourage women to get mammograms where the Native "community" includes elder women and breast cancer survivors, tribal newspapers or tribal media, and tribal clinics, and f) Community Health Representatives (CHRs) already present in the community can play an active role in dissemination of breast cancer and mammography information.

Conclusion: We have been able to build the infrastructure of the project through the provision of trainings, recruitment of project staff, and volunteers. We also have worked toward building a strong basis of collaboration and trust among the four major partners; OUHSC, the tribal clinic, the tribal government, and community members. This was accomplished by having monthly steering committee meetings, by taking time to explain research findings in lay language, and by allowing the steering committee members to reflect on the research results as we are moving forward with the project implementation. Finally, through our participation in various community/outreach projects we are continually gaining credibility within the local AI community and we are becoming more visible. These activities have further led to building trust and gaining entry into the community, both of which are critical steps to implementing an effective community-based participatory breast cancer screening program.

COMBINED MOLECULAR MRI AND IMMUNO-SPIN-TRAPPING FOR IN VIVO DETECTION OF MEMBRANE-BOUND RADICALS IN MOUSE GL261 GLIOMAS

Presenter: Rheal A. Towner, PhD

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Abstract: Free radicals associated with oxidative stress play a major role in cancer. By combining immuno-spin-trapping (IST) and molecular magnetic resonance imaging (mMRI), *in vivo* levels of membrane-bound radicals (MBR) were detected within GL261 gliomas in mice. DMPO (5,5-dimethyl pyrroline N-oxide) was administered (i.p.) over 5 days prior to the administration (i.v.) of an anti-DMPO probe (anti-DMPO antibody covalently bound to an albumin (BSA)-Gd (gadolinium)-DTPA (diethylene triamine penta acetic acid)-biotin MRI contrast agent) to trap MBR. MRI was used to detect the presence of the trapped anti-DMPO-MBR adducts by either a significant increase (p<0.001) in MR signal intensity or a significant decrease (p<0.001) in T1 relaxation, measured as %T1 change. *In vitro* assessment of the anti-DMPO probe indicated a significant decrease (p<0.0001) in T1 relaxation in GL261 cells that were oxidatively stressed with hydrogen peroxide, compared to control samples. Fluorescently-labeled streptavidin which located the anti-DMPO probe in excised brain tissues, indicating elevated fluorescence only in tumors from mice administered the anti-DMPO probe. This is the first report regarding the detection of *in vivo* levels of MBR in gliomas.

PRIMARY CNS EWING SARCOMA: A REPORT OF 2 CASES

Presenter: Katherine A. VandenHeuvel, MD

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Introduction: Pediatric small round blue cell tumors of the central nervous system (CNS) include several families of malignant tumors. Primary Ewing's sarcoma/peripheral primitive neuroectodermal tumor (ES/pPNET) of the CNS is a rare entity and we report two cases here.

Case 1: The patient is a 35 month-old girl who presented with partial seizure involving left facial twitching and lip smacking. MRI showed a large frontal, cortically-based, well circumscribed, largely solid, enhancing mass that abutted the meninges and caused moderate peritumoral edema. Grossly, the tumor was largely solid but contained a small centrally located cystic space. Histologically, it was featured by sheets of small blue cell tumor in a background of collagenous fibers suggestive of a sarcoma.

Case 2: The patient is a 28 month-old boy who presented with left side weakness, unsteady gait, and frequent falls. MRI showed a largely cystic frontotemporal mass touching the meninges and contained a small enhancing solid nodule. The tumor caused midline shift and mild peritumoral edema. Histologically, it was composed of solid sheets of small blue cells with occasional perivascular arrangement but no intervening collagen fibers. The histological features suggested a primitive neuroectodermal tumor (PNET) or ependymoma.

Special studies: For both cases, immunohistochemistry for CD99 showed strong membranous staining. Immunohistochemistry on Case 2 was suggestive of a central PNET. Both tumors were positive on PAS stain but negative on PAS with diastase. EWSR1 translocations were demonstrated by FISH.

Discussion: ES/pPNET tumors are rare primary tumors in the CNS and it is important to recognize them for appropriate treatment. Radiographically, they are typically circumscribed tumors, sometimes connected to the meninges. Histologically, the differential diagnosis includes primary and metastatic sarcoma, central PNET and medulloblastoma, ependymoma, metastatic neuroblastoma, and, less likely, atypical teratoid/rhabdoid tumor and hematopoietic tumors. The second case that we are reporting here is particularly challenging as it possesses some histologic and immunohistochemical features of central PNET and ependymoma. A high index of suspicion is mandatory for diagnosis. Immunohistochemistry for CD99 in combination of PAS stain with and without diastase provide an efficient and inexpensive mean to avoid misdiagnosis and FISH is a valuable adjunct for diagnosis.

DEVELOPMENT OF A GENERAL FRAMEWORK FOR EFFECTIVE TRANSLATION OF IN VITRO SYNERGISTIC COMBINATION INTO IN VIVO SYNERGY USING A SYSTEMIC MODELING APPROACH

Presenter: Karina Vega-Villa, PhD

Karina R. Vega-Villa, Michael Ihnat, Sukyung Woo
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Purpose: Failure of identifying optimal dosing regimen is often responsible for failed or inconclusive clinical evaluation of combination cancer therapy, and selecting synergistic combination doses remains a great challenge. The information from well-designed in vitro and preclinical animal drug combination studies - which include dose, pharmacokinetics (PK), efficacy, synergism/antagonism, and schedule dependence – can significantly contribute to the success of drug combination clinical trials. However, general methodologies for translating in vitro combination effects into preclinical and clinical in vivo doses are lacking. This study aims to develop a systemic approach for effective in vitro-in vivo translation by the combined efforts of experimental data and computational modeling.

Methods: Erlotinib and CLEFMA, a novel curcuminoid, against erlotinib-resistant NSCLC (H441) was used as a proof-of-concept drug combination for this study. The key components of the framework include a) evaluation of in vitro combination effects of two drugs and estimation of the interaction parameter (Ψ) that defines the nature of drug interaction; b) in vivo PK information of two drugs in plasma and tumor that was obtained from the literature and characterized by compartmental PK models; and c) in vivo inhibitory effects of each drug alone on tumor growth in xenograft mice, which were described by a modified Simeoni model. The final integrated model was then used to describe combined in vivo effects by incorporating the interaction parameter, thereby predicting optimal combination doses.

Results: In vitro combined effects of two drugs were fitted to 3-dimensional response surface model and suggested to be synergistic (Ψ = 0.92). Erlotinib PK in tumor-bearing mice following oral administration was described using a two-compartment model and CLEFMA PK following intravenous administration was simulated. Plasma-to-tumor distribution ratio was 0.6 for erlotinib and 0.36 for CLEFMA and tumor drug concentrations were used as a driving force for the observed inhibitory effects on tumor growth in vivo to closely mimic in vitro effective concentrations. The tumor progression in non-treated mice was depicted by an exponential growth followed by a linear growth. In treated mice, the combined inhibitory effect was described as a function of the tumor drug concentrations and the interaction parameter Ψ.

Conclusion: The present study lays out the strategy and tactics for translating in vitro synergy into maximal in vivo synergy. The developed approach can be used to better design preclinical experiments in xenograft model in a rational manner after in vitro combination studies, and to select the most advantageous in vivo combination doses and schedules for maximal synergy, thereby facilitating early anticancer drug development.

THE EFFECT OF E-CIGARETTE SAMPLING ON SMOKING BEHAVIOR AND MOTIVATION AND CONFIDENCE TO QUIT SMOKING

Presenter: Theodore Wagener, PhD

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Abstract: What effect e-cigarette (EC) use will have on smoking behavior and motivation and confidence to quit smoking is currently in question. To examine this question, we recruited 20 non-treatment seeking smokers (80% white, 60% female, Mage=40.1y, Mcpd=18.6, Mfagerstrom=5.1), naïve to ECs, to participate in a three-phase, exploratory study. In phase 1 (Baseline), participants completed baseline demographic, smoking history, and smoking thoughts and behaviors questionnaires; phase 2 (Sampling) included sampling 3 different popular EC brands (bluCig, ProSmoke, and SmokeTip) and own brand cigarette (OBC), with pre- and post-measures of product liking/satisfaction and motivation/confidence; during phase 3 (ad libitum use), participants were sent home with a 1-week supply of their preferred EC and asked to use it ad libitum and then completed follow-up questionnaires 1-week post sampling. 16 participants completed all phases of the study. During sampling, on a scale from 1 "not at all" to 10 "very much", OBC were rated as being the most liked/enjoyed (M=8.6, SD=1.8), satisfying (M=7.3, SD=3.3), and effective in reducing urges/craving (M=8.7, SD=1.7), p<.05. Of the ECs, no significant differences were found between brands but generally bluCig was found to be the preferred brand across all three domains: like/enjoy [bluCig M=6.6 (SD=2.4), ProSmoke M=4.7(SD=2.5), SmokeTip M=5.2 (SD=2.7)], satisfying [bluCig M=6.6 (SD=2.6), ProSmoke M=5.2(SD=2.9), SmokeTip M=5.0 (SD=2.8)], and effective [bluCig M=7.2 (SD=2.1), ProSmoke M=6.2(SD=2.4), SmokeTip M=6.1 (SD=2.4)]. bluCig was the brand that was selected by the most participants for the ad libitum phase (bluCig=63.2%, ProSmoke=26.3%, SmokeTip=10.5%). EC sampling led to a significant increase (p=.001) in "confidence to quit" smoking but not in "wanting to quit." However, ad libitum use of preferred EC brand for 1-week led to a significant increase in "wanting to quit" (p=.01). Confidence to quit also continued to increase from end of sampling to end of ad libitum use, but it was not significant. Number of cigarettes per day decreased significantly (p=.001) from baseline (M=16.5, SD=5.0) to end of ad libitum use (M=9.3, SD=6.7).

E-CIGARETTES: THEIR EFFECTS ON SMOKING BEHAVIOR, PULMONARY FUNCTIONING, AND MOTIVATION AND CONFIDENCE TO QUIT SMOKING

Presenter: Theodore Wagener, PhD

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Abstract: What effect e-cigarette (EC) use will have on smoking behavior and motivation and confidence to quit smoking is currently in question. To examine this question, we recruited 20 non-treatment seeking smokers (80% white, 60% female, Mage=40.1y, Mcpd=18.6, Mfagerstrom=5.1), naïve to ECs, to participate in a three-phase, exploratory study. In phase 1 (Baseline), participants completed baseline demographic, smoking history, and smoking thoughts and behaviors questionnaires. In phase 2 (Sampling), participants sampled 3 different popular EC brands (BluCig, ProSmoke, and SmokeTip) and their own usual brand of cigarette (OBC), and completed pre- and post-measures of product liking/satisfaction, motivation/confidence to quit smoking, and pulmonary functioning (spirometry). Each sampling period was separated by 60 minutes and product sampling occurred in a counterbalanced fashion. Before completing the sampling phase, participants were required to maintain 15-hour abstinence that was verified by expired breath carbon monoxide (CO ≤15ppm). In phase 3 (ad libitum use), participants left the laboratory with a 1-week supply of their preferred EC and asked to use it ad libitum and then were asked to complete follow-up questionnaires by phone 1-week post sampling. Results indicated that during sampling, pulmonary function tests (FEV1/FVC) showed no change after EC sampling but a significant reduction in pulmonary functioning (approximately 2%) following OBC sampling ($p<.05$). Regarding product liking and satisfaction, on a scale from 1 "not at all" to 10 "very much", participant's rated their own cigarette brand as being the most liked/enjoyed, satisfying, and effective in reducing urges/craving, compared to ECs (ps<.05; see Table 1). Though no significant differences were found between ratings of different EC brands (many approached significance in this small N study), BluCig was overwhelmingly selected as the EC brand to take home for the ad libitum use phase of the study (63%). EC sampling led to a significant increase ($p=.001$) in "confidence to quit" smoking but not in "wanting to quit." However, ad libitum use of preferred EC brand for 1-week led to a significant increase in "wanting to quit" ($p=.01$). Confidence to quit also continued to increase from end of sampling to end of ad libitum use, but it was not significant. Number of cigarettes smoked per day also decreased significantly ($p=.001$) from baseline (M=16.5, SD=5.0) to end of ad libitum use (M=9.3, SD=6.7). This study provides provisional evidence that 1) using ECs, at least after an initial trial, does not lead to worsening of smoker's lung functioning, 2) EC use by smokers who are not seeking treatment, can lead to significant reductions in daily cigarette consumption and increased motivation and confidence to quit smoking, and 3) BluCig was the most preferred brand of EC.

DOCOSAHEXAENOIC ACID (DHA) INCREASES HEME OXYGENASE -1 (HO-1) EXPRESSION BY ENHANCING BTB AND CNC HOMOLOGY 1 (BACH1) DEGRADATION IN HUMAN CANCER CELLS

Presenter: Shuai Wang

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Abstract: DHA (22:6, n-3) is a long chain n-3 polyunsaturated fatty acid that has been shown to have anticancer activity in various experimental model systems, likely through an enhanced lipid peroxidation. HO-1 is one of the rate-limiting enzymes in heme catabolism, which catalyzes the stereospecific degradation of heme to biliverdin and is considered a cytoprotective antioxidant enzyme. The effect of DHA on HO-1 expression in human cancer cells has never been investigated. This study characterized DHA-induced HO-1 expression using A2780 (human ovarian cancer) cells as a model system. DHA enhanced HO-1 gene expression in a time- and concentration-dependent manner with maximum induction at 21 hours of treatment. This increase in HO-1 expression induced by DHA can be reversed by the antioxidant N-acetyl Cysteine (NAC), suggesting the involvement of oxidative stress. This was confirmed by direct measurement of lipid peroxide levels after DHA treatment. Using an HO-1 gene promoter reporter construct, we identified two ARE elements that mediate the DHA-induced increase in HO-1 gene transcription, with the distal ARE being most effective. Knockdown of Nrf2 expression compromised the DHA-induced increase in HO-1 gene transcription, indicating the importance of the Nrf2 pathway in this event. Interestingly, both the protein levels of Nrf2 and its suppressor keap1 and the interaction of these two proteins remained unchanged upon DHA treatment in our model system. Further studies demonstrated that DHA reduces nuclear Bach1 (a transcriptional repressor known to bind to AREs) protein expression and the binding of Bach1 to the ARE elements in the HO-1 gene promoter. In contrast, DHA enhanced Nrf2 binding to the ARE elements in the HO-1 gene promoter without affecting nuclear Nrf2 protein expression levels. Pretreatment with the proteasome inhibitors MG132 or Bortezomib reversed the DHA-induced attenuation of nuclear Bach1 protein expression and increase in HO-1 gene transcription, indicating that DHA promotes Bach1 degradation thereby enhancing HO-1 expression. These results demonstrate that Bach1 degradation is critical to the DHA-induced increase in HO-1 expression in human ovarian cancer cells.

LPA-MEDIATED PHOSPHORYLATION OF P130CAS VIA Gα_{i2} AND SRC INDUCES INVASIVE MIGRATION OF OVARIAN CANCER CELLS

Presenter: Jeremy Ward

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Abstract: Ovarian cancer is the most deadly gynecological cancer, with previous studies implicating lysophosphatidic acid (LPA) in the progression of approximately 90% of all ovarian cancers. Nevertheless, the majority of the mechanisms through which LPA promotes ovarian cancer progression remain to be fully elucidated. Therefore, the underlying theme of our research is to identify novel LPA-activated signaling nodes that can be targeted for therapy in ovarian cancer. To this end, recent studies in our lab have identified p130Cas, a scaffold protein, is tyrosine phosphorylated in an LPA-dependent manner in ovarian cancer cells. p130Cas, upon tyrosine phosphorylation, recruits an array of signaling molecules that can promote tumor cell proliferation, survival, and metastasis and its overexpression has been linked to a significant decrease in overall survival in ovarian cancer patients, indicating the likely importance of LPA-mediated phosphorylation of p130Cas in ovarian cancer progression.

Oncogenic signaling by LPA involves the activation of at least six LPA-specific G protein-coupled receptors (LPARs). Currently, the majority of pathological effects of LPA-mediated signaling in ovarian cancer are thought to be mediated via the three Edg-family members. Relatedly, our present study identified LPAR1 (Edg-2) as the major facilitator of p130Cas phosphorylation in the ovarian cancer cells tested. Furthermore, previous studies have demonstrated that LPARs are coupled to the α-subunits of the heterotrimeric G protein families Gi, Gq, G12/13. Our current work identifies Gα_{i2} as the key G protein mediating tyrosine phosphorylation of p130Cas while revealing the G12-family inhibits tyrosine phosphorylation of p130Cas. Due to the involvement of both the Gi and G12 families in LPA-mediated migration, our study tentatively suggests a unique spatiotemporal coordination of signaling involving both the Gi and G12 families in order to facilitate invasive-migration of ovarian cancer cells. Moreover, our study demonstrates p130Cas phosphorylation is dependent on the tyrosine kinase, Src and can be potently inhibited with the FDA-approved Src inhibitor, Bosutinib. Furthermore, our current work indicates Src activation and subsequent p130Cas phosphorylation is the result of a direct activation of Src via Gα_{i2} and is Ras-independent.

Finally, using p130Cas-specific siRNA, we demonstrate p130Cas is a necessary downstream component of LPA-Gαi2-induced migration and collagen-1 invasion of ovarian cancer cells. What is more, we demonstrate Gα_{i2}-p130Cas signaling, independent of exogenous LPA, can induce collagen-1 invasion and may utilize EMT to evoke this effect in ovarian cancer cells. Overall, our study is the first to establish the LPA-LPAR1- Gα_{i2} -mediated stimulation of p130Cas is involved in invasive migration of ovarian cancer cells.

OBESITY PREVALENCE AMONG LOW-INCOME CHILDREN IN OKLAHOMA WIC, 2005-2010

Presenter: Ashley Weedn, MD

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Background: The prevalence of childhood obesity in preschool-aged children has doubled over the past 30 years. National WIC data indicate a stabilization in obesity prevalence in low-income preschool children from 2003-2008, except among American Indians, whose obesity rates continued to climb.

Objectives: To determine the prevalence of obesity in low-income preschool children in Oklahoma, to identify disparities in obesity among four major race/ethnic groups, and to describe obesity prevalence from 2005-2010.

Methods: Subjects included 218,488 children aged 2-4 years who participated in the Oklahoma WIC program. Logistic regression identified disparities in obesity among four race/ethnic groups and trends in obesity prevalence from 2005-2010.

Results: Disparities in obesity by race/ethnicity were evident with prevalence highest in Hispanics and lowest in African Americans. As a group, boys were more obese than girls ($p < .0001$); however, obesity prevalence increased among girls from 2005-2010 ($p=.0004$). Among race/ethnic groups, no differences in obesity trends were seen in girls; however, African American boys increased in obesity prevalence (OR: 1.05; 95% CI: 1.02-1.08) while boys in other race/ethnic groups showed no change.

Conclusions: In contrast to national WIC trends for low-income American Indian preschool children, obesity is not increasing in American Indians participating in Oklahoma WIC. Recent studies indicate a leveling off in obesity prevalence among low-income preschool children; however, in Oklahoma, obesity is increasing among certain subgroups of low-income preschool children.   These findings suggest a need for targeted obesity interventions in Oklahoma WIC youth.

MODELING PEDIATRIC CANCERS IN ZEBRAFISH

Presenter: Kyle West

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Background: T cell cancers are relatively common pediatric malignancies, with T cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LBL) both afflicting hundreds of US children each year. However, because childhood cancer is infrequent overall, biologic samples are not abundant. Likewise, small patient cohorts limit the feasibility of testing multiple new agents at any time in clinical trials. Animal models are tools to understand cancer's causes and to pilot new therapies. Zebrafish (Danio rerio) are small vertebrates, and since they possess a thymus, they can also develop T cell cancer. In fact, several D. rerio T cell cancer models already exist (Langenau, Science, 2003; Chen, Leukemia, 2007; Frazer, Leukemia, 2009; Gutierrez, J Exp Med, 2011) that have yielded numerous insights into T-ALL oncogenesis. These models permit studies of how T cell cancers develop and what governs their progression at the molecular level. Moreover, they are useful for pre-clinical therapeutic testing.

Objectives: To use zebrafish T cell cancer models to: (i) understand the genetic and transcriptional abnormalities that permit normal thymocytes to become malignant, (ii) determine molecular characteristics imparting particularly aggressive features to T-ALL and T-LBL, and (iii) find new medicinal agents effective in treating human T cell cancer.

Design: Samples from T cell cancer-bearing fish have been used for genetic mapping, transplantation assays, array comparative genomic hybridization, and RNA microarray analyses. Also, new therapeutics have been tested in pre-clinical 'immersion-assays' using living zebrafish with T cell cancer.

Results: We have identified candidate genes implicated in either de novo oncogenesis or disease progression. Furthermore, investigational agents have been found with in vivo efficacy against zebrafish T-ALL and T-LBL.

Conclusion: Zebrafish are a tractable organism to model human T cell cancer. On-going studies in these animals are informing our understanding of T-ALL / T-LBL oncogenesis, progression, and treatment responses.

ZINC AT NON-CYTOTOXIC CONCENTRATIONS UP-REGULATES HEME OXYGENASE-1 (HO-1) EXPRESSION THROUGH THE NRF-2 SIGNALING PATHWAY IN HUMAN CANCER CELLS

Presenter: Jing Xue

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Abstract: HO-1 is an inducible phase II detoxifying enzyme in eukaryotic cells that protects cells from various types of cellular stress. However, in cancer cells, HO-1 can increase chemo-resistance and is considered a target for cancer therapy. We have previously demonstrated that zinc ionophores induce apoptotic cell death in human cancer cells, indicating the importance of zinc ions in mediating cancer cell viability. This study investigated the effects of zinc on HO-1 expression in cancer cells in order to understand whether HO-1 is involved in zinc's anticancer activity. We found that zinc at non-cytotoxic concentrations (50-100µM) induces HO-1 expression in MDA-MB-231 (human breast cancer cell line) and A2780 (human ovarian cancer line) cells. The induction of HO-1 by zinc is both concentration- and time-dependent with initial induction at 4 hours of treatment, maximum induction at 8 hours and a rapid decline thereafter. Using a human HO-1 gene promoter reporter construct we identified two antioxidant response elements (AREs) that mediate the zinc-induced increase in HO-1 gene transcription, with the distal ARE being more effective, suggesting that the nuclear factor (erythroid-derived 2)-like 2(Nrf2) signaling pathway is involved in this event. This was supported by the finding that knockdown of Nrf2 expression compromised the zinc-induced increase in HO-1 gene transcription. Furthermore, upon treatment with zinc Nrf2 protein expression was increased and Nrf2 binding to the AREs was enhanced, further confirming this assumption. Pretreatment with antioxidants such as trolox and vitamin E could not attenuate zinc-induced HO-1 expression, suggesting that this induction is not dependent on oxidative stress. On the other hand, the increase in HO-1 gene transcription induced by zinc can be enhanced by the addition of clioquinol, a zinc ionophore, and reversed by pretreatment with N-Acetyl Cysteine (NAC) and TPEN, two known zinc chelators, indicating that the increase in cellular zinc levels is responsible for the induction. This study demonstrates that zinc is an inducer of HO-1 expression in cancer cells, suggesting that the combination of zinc ionophores and HO-1 inhibitors may be a new strategy to effectively kill cancer cells.

UP-REGULATION OF ORGANIC ANION TRANSPORTING POLYPEPTIDE (OATP) 1B3 TRANSPORT ACTIVITY BY PROTEASOME INHIBITION

Presenter: Wei Yue, PhD

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Purpose: Organic anion transporting polypeptide (OATP) 1B3 is hepatic transport protein that mediates uptake of a diverse array of endogenous compounds and drugs, including statins and many anti-cancer drugs, from blood into the liver. While under normal circumstances OATP1B3 is primarily expressed in the liver, the protein is aberrantly expressed in various cancers. Limited information exists about the regulation of the transport activity of OATP1B3. Due to the important role of the ubiquitin-proteasome pathway in the regulation of cellular processes and its relationship to numerous diseases, the proteasome has emerged as a new therapeutic target. Bortezomib is the first-in-class proteasome inhibitor for cancer therapy. The aim of this study is to determine the role of the ubiquitin-proteasome pathway in OATP1B3 degradation, and to assess the impact of proteasome inhibitors on OATP1B3 transport activity.

Method: HEK293 cells over-expressing OATP1B3 (HEK293-OATP1B3) were treated with the proteasome inhibitor MG132 (10 μM) or bortezomib (250 nM) for 2 hours. Protein levels of ubiquitin-conjugated proteins and OATP1B3 were determined by immunoblot of ubiquitin and OATP1B3, respectively. The mRNA levels of OATP1B3 were determined by real-time RT-PCR. Kinetic parameters (K_m and V_{max}) of OATP1B3-mediated [^{3}H]CCK-8 uptake in HEK293-OATP1B3 cells were estimated by nonlinear least squares regression using WinNonlin (Pharsight); values were compared among MG132, bortezomib and vehicle control treatments.

Results: The ubiquitin-conjugated proteins were significantly increased in MG132- and bortezomib-treated HEK293-OATP1B3 cells compared to the control. Following proteasome inhibition, protein levels of OATP1B3 in HEK293-OATP1B3 cells were markedly increased while mRNA levels of OATP1B3 were not affected. These results indicated that the ubiquitin-proteasome pathway is involved in the degradation of OATP1B3. The increase in OATP1B3 protein levels following proteasome inhibition was most likely regulated in a post-translational manner. Proteasome inhibition in HEK293-OATP1B3 cells resulted in a significant increase in accumulation of [^{3}H]CCK-8 (1 μM, 3 min), a specific substrate of OATP1B3, and a pronounced increase in V_{max} and decrease in K_m of CCK-8 transport by OATP1B3 (Table 1).

Conclusions: Proteasome inhibition up-regulated OATP1B3 transport activity. These studies provide a novel mechanism for modulation of uptake of OATP1B3 substrates and emphasize the importance of proteasome inhibitors as a potential determinant for OATP1B3-mediated hepatotoxicity and the therapeutic effect of anti-cancer drugs that are OATP1B3 substrates.

Table 1. Kinetic parameters of OATP1B3-mediated CCK-8 transport in control, MG132- and bortezomib-treated HEK293-OATP1B3 cells

Treatment	K_m (μM)	V_{max} (pmol/mg protein/min)
CTL	4.1 ± 0.8	60.6 ± 4.7
MG132 (10 μM, 2 h)	0.6 ± 0.1	171.8 ± 8.8
Bortezomib (0.25 μM, 2 h)	0.5 ± 0.1	159.1 ± 9.0

Shared Resources

Biospecimen Acquisition Core and Bank

About the Core

The SCC Biospecimen Acquisition Core and Bank was established in 2006 when the SCC assumed management of the Dawn Hope Tissue Bank, a large collection of gynecologic tissue samples. Since that time the Core has provided specimen collection, storage and processing services to SCC members and other investigators. The Core's Biospecimen Bank currently contains over 30,000 aliquotted samples collected since 2008, including tissue, blood, plasma, serum, cell and buccal samples. The Core utilizes an IRB-approved Universal Consent that allows patients at SCC, OU Physicians or OU Medical Center to donate tissue or blood to the Biospecimen Bank. Over 3,500 patients have consented to participate since 2008. The Core has especially 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 a large and active clinical research program at the SCC. 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, for which the SCC was the lead tissue site in each. A dedicated PK processing room supports the SCC's Phase I clinical trials program.

In 2012 the SCC was selected as a Tissue Source Site for The Cancer Genome Atlas (TCGA) Project. TCGA researchers are identifying the genomic changes in more than 20 different types of human cancer. By comparing the DNA in samples of normal tissue and cancer tissue taken from the same patient, researchers can identify changes specific to that particular cancer. By connecting specific genomic changes with specific outcomes, researchers will be able to develop more effective, individualized ways of helping each cancer patient.

The Core's main facility is on the fourth floor of the Stanton L. Young Biomedical Research Center (BRC) on the OUHSC campus. A satellite facility on the third floor of the SCC building is dedicated to supporting the SCC's Phase I clinical trials 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 appropriate specimens are not available in the Biospecimen Bank, Core staff will help facilitate the procurement of specimens from the appropriate sources. The Core also supports protocol-driven specimen collection for specific research projects.

Core Information Systems

In conjunction with the Cancer Center's Clinical Trials Office, the Biospecimen Core uses a HIPAA and 21 CFR Part 11 compliant clinical trials management system (Velos eResearch). An integrated sample inventory system is used to catalogue banked specimens (Velos eSample). Data are stored on a secure server with access limited to key protocol personnel. A Cancer Center database analyst provides support as needed in the construction of custom database forms, reports and queries.

Contact Information

For more information about the Core please contact:

David Brown
Supervisor, Biospecimen Core
Phone: 271-8001, Ext. 48475
david-brown@ouhsc.edu

Biostatistics Core

About the Core

The Biostatistics Core at the Stephenson Cancer Center provides SCC 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

Scientific Director: Kar-Ming Fung, MD, PhD

About the Core

The goal of the Cancer Tissue Pathology Core is to provide high-quality tissue processing, histology and staining services to SCC 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 SCC 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.

The goal of the Cancer Tissue Pathology Core is to provide high-quality tissue processing, histology and staining services to SCC members and other investigators.

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 about the Core please contact:

Muralidharan Jayaraman, PhD
Director of Research Core Operations
Email: muralidharan-jayaraman@ouhsc.edu
Phone: (405) 271-6890

Cancer Functional Genomics Core

Scientific Director: Danny Dhanasekaran, PhD (Interim)

About the Core

Gene expression variability across the genome has significant impact on understanding the progress and prognosis of cancer. The Cancer Functional Genomics Core at the Stephenson Cancer Center offers cutting-edge technology that can provide extremely accurate and reliable expression data to support drug discovery research. The versatile Agilent SureScan Microarray Scanner system provides the ability to scan genome-wide microarray profiles. The Biorad CFX96™ Touch Real-Time PCR Detection System provides highly-reliable quantitative individual gene transcription profiling. Functional analysis of proteins using biochemical assay can be evaluated with the Perkin Elmer EnVision® Multilabel Reader. Other instruments housed in the facility include the Biorad Experion™ Automated Electrophoresis Station and Agilent 2100 Bioanalyzer.

Services Offered

- Array Scanning and Quantification
- Reverse Proteomics Array (coming March 2013)
- Real-Time PCR
- Multimodal Assay Screening
- DNA / RNA / Protein Purity Analysis on a Chip

Contact Information

For more information about the Core please contact:

Muralidharan Jayaraman, PhD
Director, Research Core Operations
Muralidharan–Jayaraman@ouhsc.edu

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

For more information about the Core please contact:

Ingrid Block, RN, MS, CNS
Director, Clinical Trials Office
Phone: 405-271-8777, ext. 48160
Email: ingrid-block@ouhsc.edu

Molecular Imaging Core

About the Core

The Molecular Imaging Core provides non-invasive optical imaging services to Stephenson Cancer Center members and other investigators at the OU Health Sciences Center and neighboring institutions. The Core includes the following equipment:

- IVIS Spectrum Imaging System – provides a wide range of imaging capabilities including bioluminescence, fluorescence, and near-infrared imaging with 3D anatomical overlay
- Carestream In-Vivo Xtreme Imaging System – specifically designed for researchers seeking high-sensitivity luminescence, fluorescence, radioisotopic, and radiographic imaging
- Leica Fluorescence Stereo Microscope
- INVIVO 400 and 500 Hypoxia Workstations

Services Offered

1. Training and consultation
2. Preclinical tumor models
3. Experimental design and data analysis

Contact Information

For more information about the Core please contact:

Rajagopal Ramesh, PhD
Director, Molecular Imaging Core
Rajagopal-ramesh@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

For more information on how we may help plan your study utilizing the small animal MRI system, contact our staff via email phone fax or regular mail.

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
(405) 271-2469

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: lmbcr_help@ouhsc.edu

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

Proposal Services

The Proposal Services Core is a service that is available to all SCC 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
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

The Special Populations Core at the Peggy and Charles Stephenson Cancer Center provides the following services to Cancer Center investigators to promote collaborations with American Indian and other minority populations:

- Consultation services as studies that may involve minority participants are being planned;
- Identification of appropriate partners, preferably as early as possible in the planning process;
- Identification of appropriate Cancer Center investigators in response to tribal requests for research partners to pursue tribally-initiated research questions;
- Facilitation of meetings between center investigators and potential minority partners;
- Consultations 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 resolutions of support;
- Consultation in preparing IRB applications (for OU IRB and tribal and Indian Health Service IRBs);
- Ongoing assistance in managing community-university relationships as the study is being conducted;
- Consultations about concluding studies and reporting findings back to tribes, tribal organizations, and participants (as appropriate);
- Nurturing awareness of cancer health disparity research on campuses;
- Serve as the primary point of contact between the Cancer Center and Oklahoma tribes, tribal health systems, 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: 405-271-4272, ext. 42732
lancer-stephens@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
Ralf Janknecht, PhD

Program Members

Naushad Ali, PhD

Hong Chen, PhD

Danny Dhanasekaran, PhD

Gary Gorbsky, PhD

Marie Hanigan, PhD

Robert Hurst, PhD

Guangpu Li, PhD

HK Lin, PhD

Hiryuki Matsumoto, PhD

Lorin Olson, PhD

Augen Pioszak, PhD

Lawrence Rothblum, PhD

William Sonntag, PhD

Kent Teague, PhD

Leonidas Tsiokas, PhD

Lauren Zenewicz, PhD

Zhizhuang (Joe) Zhao, PhD

Ira Blader, PhD

David F. Crawford, MD, PhD

Kimble J. Frazer, MD

Courtney Griffin, PhD

Eric Howard, PhD

Jens Kreth, PhD

Shibo Li, MD

Jialing Lin, PhD

Blaine Mooers, PhD

Roberto Pezza, PhD

Lurdes Queimado, MD, PhD

Ping Song, PhD

Xiao-Hong Sun, PhD

Rheal Towner, PhD

Christopher West, PhD

Xin Zhang, MD, PhD

Women's Cancers Research Program

The focus of the Women's 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 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 Leaders
Scott McMeekin, MD
Doris Benbrook, PhD

Program Members

Sulaiman Aldoohan, PhD
William Dooley, MD
William Hildebrand, PhD
Lisa Landrum, MD
Robert Matts, PhD
Kathleen Moore, MD
Dana Rundle, PhD
Joan Walker, MD
Rosemary Zuna, MD

Wei-Qun Ding, PhD
Jihee Ha, PhD
Sanam Husain, MD
Robert Mannel, MD
Marianne Matzo, PhD, RN
Katherine Moxley, MD
Leon Spicer, PhD
Dee Wu, PhD

Gastrointestinal Cancers Research Program

Investigators in the Gastrointestinal Cancers Research Program study the role that epithelial and mesenchymal stem cells play in the development, progression and metastasis of tumors of the gastrointestinal system, especially the colon, pancreas, liver, and esophagus. Another program goal is increasing the understanding of the role microRNAs play in tumor initiation. The program also focuses on the detection of plasma biomarkers for stem-cell related proteins in order to develop novel diagnostics for early cancer detection. Research in the Gastrointestinal Cancers Research Program includes laboratory-based basic, translational and preclinical research members in addition to an active clinical research program that encompasses phase I, II and III clinical trials.

Program Leader
Courtney Houchen, MD

Program Members

Jay Hanas, PhD	Mark Huycke, MD
Naveena Janakiram, PhD	Rashmi Kaul, PhD
Justin Merritt, PhD	Altaf Mohammed, PhD
Shubham Pant, MD	Jagan Patlolla, PhD
Felicia Qi, PhD	Osama Qubaiah, MD
CV Rao, PhD	Sripathi Sureban, PhD
Ken Vega, MD	Hiroshi Yamada, PhD

Experimental Therapeutics Research Program

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

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

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

Program Leader
Rajagopal Ramesh, PhD

Program Members

Natarajan Aravindan, PhD	Shanjana Awasthi, PhD
Vibhudutta Awasthi, PhD	Kenneth Berlin, PhD
Wei Chen, PhD	Mohamad Cherry, MD
Kar-Ming Fung, MD, PhD	Hariprasad Gali, PhD
Lucila Garcia-Contreras, PhD	Roger Harrison, PhD
Franklin Hays, PhD	Terence Herman, MD
Jennifer Holter-Chakrabarty, MD	Michael Ihnat, PhD
Carla Kurkjian, MD	Hong Liu, PhD
Jian-xing Ma MD, PhD	Chance Matthieson, MD
Chuanbin Mao, PhD	Rene McNall-Knapp, MD
Anupama Munshi, PhD	Daqing Piao, PhD
Ronald Rahaim, PhD	David Schmidtke, PhD
George Selby, MD	Vassilios Sikavitsas, MD
Joel Slaton, MD	Rodney Tweten, PhD
Sukyung Woo, PhD	Jonathan Wren, PhD
Youngjae You, PhD	Wei Yue, PhD
Daniel Zhao, PhD	Ming-Hui Zou, 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 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 underserved tribal and other communities in collaborative cancer prevention and control research and strategies to reduce cancer-related health disparities

Program Leader
Mark Doescher, MD, MHS

Program Members

Laura Beebe, PhD	Paul Branscum, PhD
Janis Campbell, PhD	Marshall Cheney, PhD
Carrie Ciro, PhD	Melissa Craft, PhD, RN
Tom Darling, PhD	Randolph Deal, PhD
Kai Ding, PhD	Kathleen Dwyer, PhD, RN
Valerie Eschiti, PhD, RN	Blas Espinosa-Varas, PhD
Morris Foster, PhD	Jack Friedman, PhD
Xun Ge, PhD	Henry Hallford, PhD
Robert Hamm, PhD	Barbara J. Hotzclaw, PhD
Elaine Hsieh, PhD	Valarie Jernigan, DrPH
Lori Jervis, PhD	Ahsan Khan, MD
Allen W. Knehans, PhD	Fritz Laux, PhD
Sheryl Magzamen, PhD, MPH	James Mold, MD
Zsolt Nagykaldi, PhD	Carol Rogers, PhD
Dorothy Rhoades, MD, MPH	Christina Shay, PhD
Carolin Showers, PhD	Susan Sisson, PhD, CHES
Patsy Smith, PhD	Paul Spicer, PhD
Julie Stoner, PhD	Eleni Tolma, PhD
Sara Vesely, PhD	Ted Wagener, PhD
Joe Watkins, PhD	Norman Wong, PhD
Fawn Yeh, PhD	

Cancer Center Researchers & Research Interests

Naushad Ali, PhD

Department of Medicine, Section of Digestive Diseases Nutrition, SCC

Research Interest:

A. HCV-induced liver cancer:

The overall goal of PI's research is to understand molecular mechanism of hepatitis C virus (HCV)-induced initiation of hepatocellular carcinoma (HCC), the third most common cause of cancer-related deaths worldwide. The immediate goal is to identify novel targets for inhibiting tumor/cancer initiating stem cells (CSC), which are considered to be the 'seedlings' of tumor mass. Importantly, HCC risk increases to nearly 100-fold in HCV carriers with obesity and diabetes, which are fast growing in USA. The generation of hepatocytes-derived fibroblasts due to undesirable epithelial-mesenchymal transition (EMT) has been implicated in the initiation of liver fibrosis/cirrhosis, that is an important risk factor for the initiation of HCC. However, molecular mechanism of HCV-induced cirrhosis and HCC is poorly understood.

Our recent studies have revealed a positive correlation between HCV replication and expression of tumor/cancer-initiating stem cell (CSC) marker, doublecortin-like kinase1 (DCLK1). We demonstrated that DCLK1 expression tends to increase during progression of liver diseases in HCV-positive patients. Our preliminary data further suggest that normal human hepatocytes (NHH) shows high-level DCLK1 expression when cultured as spheroids in Matrigel but not as collagen monolayer. These spheroids form metastatic tumors with high abundance of DCLK1-positive cells in the xenografts. Our recent work suggests that targeting DCLK1 in liver-derived hepatoma cells is feasible and its downregulation using siRNA specifically reduces HCV replication as well as CSC-related proteins. Thus, it is possible that induction of DCLK1 by growth factors (as found in Matrigel) and/or HCV leads to reprogramming and selection of CSC-like cells. Our current goal is to isolate the sub-population and devise means to study sensitivity of these subsets (e.g. HCV-DCLK1 double positive cells) against various drugs.

B. Hepatic stem cells and liver tissue regeneration

Liver resection and orthotopic liver transplantation are usually employed in advanced stage liver diseases including HCC. The scarcity of liver donors for transplantation and lack of genetically matched hepatocytes are major obstacles for the treatment of such problems. Direct clinical applications of hepatocyte-like cells derived from embryonic, hematopoietic, and induced pluripotent stem cells are extremely premature because of their inherent limitations. Thus, the generation of an adequate supply of autologous adult liver stem/progenitor cells (S/PCs) is of great therapeutic interests. We are pursuing research to enrich and maintain stem/progenitor-like cells that may exhibit therapeutic potentials.

In summary, I have been working as a cancer investigator and will continue my research to understand initiation of tumors and devise means to attack tumor-initiating events.

Natarajan Aravindan, PhD

Department of Medicine, Section of Digestive Diseases Nutrition, SCC

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.

Laura A. Beebe, PhD

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

Research Interests: Laura Beebe is a Professor in the Department of Biostatistics and Epidemiology at the University of Oklahoma Health Sciences Center and the Director of the Oklahoma Tobacco Research Center, a center within the Peggy and Charles Stephenson Cancer Center. Dr. Beebe has significant experience in tobacco-related surveillance and evaluation research. She has served as the Principal Investigator for the evaluation of TSET-funded programs for more than 10 years, and for the past 15 years she has worked with American Indian communities to address disparities related to tobacco abuse and other cancer risk factors. Dr. Beebe is presently funded by the National Cancer Institute to study a culturally-tailored smoking cessation program for American Indians.

Janis Campbell, PhD

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

Biographical Description: Janis Campbell, PhD is an Assistant Professor of Research at the University of Oklahoma, College of Public Health, Biostatistics and Epidemiology Department for almost 5 years. Dr. Campbell previously served as Chronic Disease surveillance coordinator for nine years and for five years as a program analyst for Maternal and Child Health Services at the Oklahoma State Department of Health. Dr. Campbell has 20 years of experience working with American Indian populations and public health. Dr. Campbell was previously the Principal Investigator of the NCI-funded OU Community Networks Program. Additionally, she has published and presented nationally and internationally on health disparities, health prevention programs, and multi-level interventions. As an anthropologist by training, her work focuses on the social and cultural aspects of health disparities, combining both qualitative and quantitative methods. Dr. Campbell was the PI for CDC funded Oklahoma REACH 2010, the American Indian Centers of Excellence in the Elimination of Disparities and the Oklahoma Central Cancer Registry.

Melissa Craft, PhD, RN

College of Nursing, University of Oklahoma Health Sciences Center

Research Interests: Melissa Craft, PhD, RN is an Assistant Professor, Director of the Clinical Nurse Specialist Program, and Co-Director of the Doctor of Nursing Practice Program in the OUHSC College of Nursing. She is also an Oncology Clinical Nurse Specialist with over 30 years of experience, ranging from service as Director of Oncology Services at a large metropolitan hospital to running a high-risk breast cancer clinic, the latter which incorporated genetic counseling and testing.   Her major area of research focuses on the use of expressive writing as a distress-alleviating technique for breast cancer patients and survivors. Her research has explored the use of a reflective writing paradigm and has demonstrated improvements in self-reported quality of life. She recently completed an expressive writing/storytelling pilot study with American Indian women with gynecologic cancer, and results indicated acceptance of a brief writing intervention with benefits similar to those seen in other expressive writing studies.

With funding from a competitive Breast Cancer Research Seed Grant from the Stephenson Cancer Center, Dr. Craft and her colleague Dr. Carol Rogers, are currently implementing a study that employs a mixed methods RCT design to 1) adapt a Sign Chi Do (SCD) intervention and 2) combine it with an expressive writing activity. They will evaluate the effects of the intervention compared to informational care on fatigue, sleep, mood, quality of life, and physical activity outcomes in breast cancer patients receiving treatment. Their findings will support the preparation of an R01 competitive grant application to conduct a larger RCT testing the effect of a SCD intervention on cancer-related fatigue and sleep among women during treatment for breast cancer.

John Daum

Cell Cycle and Cancer Biology Program, Oklahoma Medical Research Foundation

Research Interests: The several ongoing projects in our 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.

Mark Doescher, MD, MSPH

Cancer Health Disparities Program, Peggy and Charles Stephenson Cancer Center

Research Interests: Mark Doescher, MD, MSPH, is Program Leader of the Cancer Health Disparities Program at the Peggy and Charles Stephenson Cancer Center and Professor of Family Medicine, Oklahoma Health Sciences Center. In his capacity as SCC Program Leader, he seeks to develop a program of research aimed at reducing the burden of cancer that is proportionately shouldered by Oklahoma's most socially and economically vulnerable groups by harnessing the collective talents of a diverse pool of researchers, clinicians, and community stakeholders across the state.

 Previously, Dr. Doescher served as the Director and PI of the Washington-Wyoming-Alaska-Montana-Idaho (WWAMI) Rural Health Research Center and the UW Center for Health Workforce Studies and as the Associate Director of the WWAMI Area Health Education Center. Recent work has focused on whether rural patients are receiving recommended therapy for breast, prostate and other types of cancers, and with colleagues he recently examined national trends in colorectal cancer screening among rural adults aged 50 and older. He is currently leading an NIH-funded research study examining exercise and patterns of health in rural communities.

 Dr. Doescher received his MD from the University of California, San Francisco and his public health degree from the University of Colorado, Denver. He completed his family medicine training at the University of Rochester/Highland Hospital residency program.

Valerie Eschiti, PhD, RN, AHN-BC, CHTP, CTN-A

College of Nursing, University of Oklahoma Health Sciences Center

Research Interests: Valerie Eschiti, PhD, RN, AHN-BC, CHTP, CTN-A, has been active in Native American communities since 1988, often employed as a nurse in health care settings serving Native people. She is a certified advanced transcultural nurse. Dr. Eschiti's program of research is focused on cancer education and behavioral change across the continuum for Native American people. She has successfully conducted cancer-related research projects using a CBPR approach in partnership with the Comanche Nation and support of the Southwest Intertribal Health Board, comprised of 7 tribes: Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita & Affiliated Tribes. She serves as a consultant to the American Cancer Society national office, providing training to tribal Community Health Representatives regarding the revised Circle of Life wellness and cancer education program for Native people. This study was funded by the Oklahoma Stephenson Cancer Center/Tobacco Settlement Endowment Trust. Dr. Eschiti is also funded by the National Institute of Nursing Research for the study, "Native Navigation across the Cancer Continuum in Comanche Nation."

Toni Finch, MSN, RN, OCN

PhD Graduate Program, College of Nursing, University of Texas at Arlington

Toni Finch, MSN, RN, OCN is a PhD nursing student at the University of Texas at Arlington and an enrolled member of Seminole Nation. Her research focus is cancer education in Native American communities of southeast Oklahoma. She is an Oncology Certified Nurse who has worked in oncology nursing since 1993. She assisted Lauri John, PhD, RN with a pilot study evaluating the quality of life of patients diagnosed with graft-versus-host disease after receiving allogeneic stem cell transplantation at Baylor Dallas. She is working with the Navigation for Indian Health research team as part of her doctoral research practicum.

Chenying Fu

Department of Physiology, University of Oklahoma Health Science Center

Research (MS)
*Project : "The cloning and expression of the IgE Cε2-4 and IgE Cε3-4，analysis of the function the fusion protein interact with FcεRⅠand preparation and identification of McAbs"

Research (PhD):
*Project : "EWI-2/PGRL physically associates with tetraspanins and regulates integrins and impaires cancer cell proliferation and movement"

Publications:
Chenying Fu, Wenqi Dong (2009). Prokaryotic expression、purification of IgE Cε3-Cε4，analysis of the function IgE Cε3-Cε4 interact with FcεRⅠand the identification of polyclonal antibody.

YIN Qing,CHEN Bai-hong,QIU Guo-zhen,FU Chen-ying,DONG Wen-qi,WEI Wei, LI Zhen,ZHU Yong,WANG Ping. Cloning and Expression of IgE Low-Affinity Receptor Prokaryotic Expression System.

QIU Guo-zhen, CHEN Bai-hong, QU Rong-mei, FU Chen-ying, DONG Wen-qi,
WEI Wei, WANG Wen-jing, WANG Ping. Cloning and Expression of the Human SH2B1β.

Jay Hanas, PhD

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

Research Interests: Jay Hanas, Ph.D., is a Professor of Biochemistry and Molecular Biology at the University of Oklahoma Health Sciences Center. His research interests are focused upon understanding disease phenotypes and their underlying gene regulatory mechanisms. His laboratory is developing serum mass profiling as a technology for early detection and monitoring of cancer and other diseases

Roger G. Harrison, PhD

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

Research Interests: 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.

Sanam Husain, MD

Department of Pathology, University of Oklahoma Health Science Center

Research Interests: I am currently an Assistant Professor at the University of Oklahoma Health Sciences in the Department of Pathology. I am trained in Anatomic and Clinical Pathology with additional advanced training in Gynecologic Pathology (equivalent to fellowship) and Surgical Pathology (equivalent to fellowship). During my training and practical sign-out experience, I developed a special interest in cervical dysplasia, the role of specific HPV genotypes involved in the pathogenesis and the progression to invasive carcinoma. There can be significant inter-observer variability in the diagnosis of CIN I and CIN 2 lesions. The goal of this study was to use objective measures using immunohistochemical stains to better categorize the squamous intraepithelial lesions so patients are managed appropriately and complications of procedures like LEEP can be avoided. I have worked closely with Dr. Rosemary Zuna who is also my mentor in the field of gynecologic pathology. Dr. Zuna's primary interest is the study of gynecologic neoplasms with an overall interest in HPV-associated carcinogenesis. Recently she has served as a study pathologist on the NCI-sponsored ALTS and SUCCEED trials that have studied cervical cancer and its precursor lesions.

My additional research interests include endometrial carcinoma, its association with obesity and hypertension and endometriosis associated malignancies.

Ralf Janknecht, PhD

Department of Cell Biology, University of Oklahoma Health Sciences Center

Research Interests: My research has centered for two decades on transcription regulation and how this relates to tumorigenesis. In addition to biochemical and cell culture studies, my laboratory has successfully employed xenograft as well as transgenic and knock-out mouse models to reveal the importance of transcription factors in tumor formation. Moreover, we have extensive experience in the field of epigenetic regulation by histone demethylases. Apart from prostate and colon cancer, our research has also focused on breast cancer.

Valarie Blue Bird Jernigan, PhD

Health Promotion Sciences, College of Public Health, University of Oklahoma Tulsa

Research Interests: Valarie Blue Bird Jernigan is an Assistant Professor of Health Promotion Sciences, College of Public Health, University of Oklahoma Tulsa. She holds a doctorate from University of California at Berkeley and attended film school at Stanford University and the San Francisco School of Digital Filmmaking. She also completed a postdoctoral fellowship at the Stanford Prevention Research Center. Dr. Jernigan is a member of the Choctaw Nation.

Dr. Jernigan's work focuses on participatory action research with Indigenous communities for social justice and improved health outcomes. She uses documentary film, photography, and social media to create innovative programs aimed at community organizing and capacity building to create health enhancing policies with tribal nations. Her more recent work addresses food insecurity and poor food environments on reservations as well as the promotion of smoke free legislation.

Sydney Martinez, MPH

College of Public Health, University of Oklahoma Health Sciences Center

Research Interests: Sydney Martinez, MPH, is a doctoral student in Epidemiology in the College of Public Health, University of Oklahoma Health Sciences Center. She also serves as Research Project Coordinator and Evaluator for the Department of Biostatistics and Epidemiology in the College of Public Health, where she is currently evaluating multiple public health prevention programs focusing on tobacco, physical activity, and nutrition. More recently she has conducted epidemiological analyses of cancer disparities among American Indians in Oklahoma. Her broad research interests lie in the area of community-based chronic disease prevention. In her dissertation research, she hopes to focus on health disparities among low-SES populations who are disproportionately affected by tobacco-related mortality and morbidity. Ms. Martinez received her Masters of Public Health in Epidemiology from the University of Oklahoma Health Sciences Center and a Bachelors of Science Degree from the University of Oklahoma in Health and Exercise Science.

James W. Mold, MD, MPH

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

Research Interests: Dr. James 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 extraordinarily 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.

Zsolt Nagykaldi, PhD

Family & Preventive Medicine, University of Oklahoma Health Sciences Center

Research Interests: Dr. Nagykaldi is an Associate Professor in the Department of Family & Preventive Medicine at the University of Oklahoma Health Sciences Center. He is also the Administrative Director and Network Coordinator of the Oklahoma Physicians Resource/Research Network (OKPRN). He holds a BS in pharmacy and a PhD in pharmacology. He also participated in a two-year Masters-level Public Health and Health Services Research didactic curriculum, as part of K08 training. Since 2001, he has been working closely with primary care practices throughout Oklahoma to improve the quality and safety of care through practice-based health services research. He has collaborated in a number of research and quality improvement projects as a PI, co-PI, or key participant, including preventive services delivery, chronic disease management, practice facilitation and redesign, patient-centered care, clinical decision-support, and the design and implementation of health information technology in various care settings.

Partnering with clinicians, he has developed 20 health IT applications that have helped improve care delivery locally or nationally. Several R&D projects aimed the design and testing of novel approaches to empowerment of patients via EHR / PHR technology, patient portals, and regional health information exchange.   He has participated in the creation of public-private partnerships around health IT, improvement of seasonal and pandemic influenza preparedness, promotion of primary care practice facilitation approaches and dissemination of practice redesign methods nationally.   He is a regular reviewer for a number of primary care peer-reviewed journals and member of various study sections at AHRQ and international research organizations. My current work includes the development and testing of a novel, goal-directed, prospective care delivery approach via a new-generation, web-based health risk appraisal tool.

Anne Pate, PhD, MPH

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

Research Interests: Anne Pate, PhD, MPH has worked as the epidemiologist for the cancer programs at the Oklahoma State Department of Health for the past eight years. She received her B.S. in science education from Taylor University, her MPH in Epidemiology of Microbial Disease from Yale University, and her PhD in Occupational and Environmental Health at the University of Oklahoma Health Sciences Center. She teaches as adjunct faculty at the College of Public Health in addition to her duties managing the cancer registry and providing epidemiologic support to the registry and the other cancer programs. Her interests include studying and improving our understanding of the health impacts, specifically cancer, from exposure to environmental contaminants.

Daqing Piao, PhD

School of Electrical and Computer Engineering, Oklahoma State University

Research Interests: Daqing Piao received the B.Sc. degree in physics from Tsinghua University in Beijing, China, in 1990, and the M.Sc. and Ph.D. degrees both in biomedical engineering from the University of Connecticut, Storrs, CT, in 2001 and 2003, respectively. From 2003 to 2005 he completed two post-doctoral training respectively in University of Connecticut with Quing Zhu and in Dartmouth College with Brain W. Pogue and Keith D. Paulsen. Prior to his post-graduate education, he also worked at Guandong Weida Medical Apparatus Group Co. from 1990 to 1994 on magnetic resonance imaging instrumentation and at Shanghai Kanglian Medical Engineering Co. Ltd. from 1994 to 1999 on biomedical applications of radio-frequency and millimeter-wave.

He joined the School of Electrical and Computer Engineering, Oklahoma State University, Stillwater, OK in 2005 as assistant professor and has been associate professor since 2011. He is senior member of Institute of Electrical and Electronics Engineers (IEEE), senior member of the Optical Society of America (OSA), senior member of the International Society of Optical Engineering (SPIE), member of American Society for Laser Medicine and Surgery (ASLMS), and associate member of Stephenson Cancer Research Center.

He has research interests in developing noninvasive or minimally-invasive modalities for cancer molecular-imaging, image-guided therapeutic intervention, and monitoring treatment response. His on-going cancer-related applied research activities include: (1) trans-rectal ultrasound guided fluorescence optical tomography for prostate cancer imaging; (2) magneto-thermo-acoustic imaging and magnetically-mediated-hyperthermia for cancer theranostics; (3) endoscopic detection of radio-tracer labeled molecular probe for cancer detection; and (4) needle-based ultra-fine fiber-optical biopsy.

Lurdes Queimado, MD, PhD

Departments of Otorhinolaryngology, Cell Biology and Pediatrics, University of Oklahoma Health Sciences Center

Research Interests: I am an Associate Professor in the Departments of Otorhinolaryngology, Cell Biology and Pediatrics and the Director of Basic and Translational Research in the Otorhinolaryngology Department 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 normal and tumor cell lines, which have been distributed all over the world. 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. Therefore, 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 by developing a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA) to map and quantify in vivo levels of DNA damage. Using PADDA, we have mapped for the first time in vivo highly mutagenic nucleotide lesions, and demonstrated a strong correlation between persistent nucleotide damage and the later establishment of mutations precisely in those nucleotides. 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 shown that: (a) Wnt/β-catenin signaling is under tight control in human normal salivary gland stem cells; (b) aberrant activation of β-catenin contributes to head and neck, salivary gland, and cervical cancers; and (c) Wnt inhibitors induce significant tumor cell death and promote differentiation in vitro and in vivo. Presently, we are particularly interested in the molecular mechanisms that regulate normal and cancer stem cell self-renewal and multi-potency. We are exploring whether the secreted Wnt proteins can be used to facilitate the expansion of normal salivary gland stem cells with the purpose of regenerating radiation-damaged salivary glands. 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.

Carol E. Rogers, PhD, RN

College of Nursing, University of Oklahoma Health Sciences Center

Research Interests: Carol Rogers, RN, PhD, is an Assistant Professor in the OUHSC College of Nursing. She has studied under nursing faculty working on the cutting-edge of funded research in survivorship care including Dr. Linda Larkey, Arizona State University, and Anna Schwartz, University of Washington. Dr. Rogers' research focuses on mind-body methods of alleviating symptoms in cancer survivors through physical activity. A major study conducted with Drs. Linda Larkey and Roger Jahnke examined the effect of a Tai Chi/Qigong exercise compared to a non-meditative exercise on fatigue, sleep, cognition, and BMI among breast cancer survivors. Findings 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.

With funding from a competitive Breast Cancer Research Seed Grant from the Stephenson Cancer Center, Dr. Rogers and her colleague Dr. Melissa Craft, are currently implementing a study that employs a mixed methods RCT design to 1) adapt a Sign Chi Do (SCD) intervention and 2) combine it with an expressive writing activity. They will evaluate the effects of the intervention compared to informational care on fatigue, sleep, mood, quality of life, and physical activity outcomes in breast cancer patients receiving treatment. Their findings will support the preparation of an R01 competitive grant application to conduct a larger RCT testing the effect of a SCD intervention on cancer-related fatigue and sleep among women during treatment for breast cancer.

Dana Rundle, PhD

Department of Chemistry, University of Central Oklahoma

Research Interests: Current research interests are in understanding the mechanisms by which SHetA2 and selected analogs are able to induce cell death. The activity and intracellular protein-protein interactions of several candidate molecules including PKC iota, PKC delta, and STAT3 are being evaluated in response to SHetA2 and several heteroarotinoid analogs.

Rheal A. Towner, PhD

Advanced Magnetic Resonance Center, Oklahoma Medical Research Foundation

Research Interests: The research in Dr. Towner's laboratory centers on developing new ways to diagnose and predict the outcome of human diseases using non-invasive imaging and spectroscopic methods. These methods also allow us to evaluate new and existing drugs and determine optimal treatment protocols for the specific disease. In his laboratory they use the techniques of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) to identify and study specific conditions of injured or diseased tissues in small animal models of disease. Their experimental approach of using MRI and MRS technology with small animal models of disease has many advantages, including the ability to investigate disease processes both in vivo, which means while the animal is alive, and in real time. Currently, they are most interested in understanding the molecular events that lead to the formation and development of cancer cells as well as the processes that cause tissue injury after the ingestion of natural toxins that can be found in contaminated food or water.

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

These same MRI methods are also used to assess anti-cancer treatments in animal cancer models and they have found a promising drug candidate that recedes tumor growth in experimental model of brain cancer. Specifically, they have used MRI methodology to evaluate an anti-glioma agent called OKN-007 in rodent gliomas, and this compound is now an investigational drug currently in human clinical trials for recurrent gliomas.

Another focus in Dr. Towner's laboratory is on the discovery of "MRI molecular targeting agents", or agents that selectively target or pinpoint tumor antigens on cancer cells and then allow the cancer cells to be visualized by MRI in live animals. By using in vivo MRI techniques to study tumors in the liver and brain of rodent models of cancer, they can simultaneously detect changes in tumor markers on the malignant cells, measure biochemical properties of the cancer cells, and determine the pathology of the tumor. They then correlate these molecular findings with progression of the disease. In fact, DR. Towner's laboratory was among the first to detect tumors in experimental animal models that express specific receptors, such as c-Met, VEGFR2 and iNOS, found in many human cancers, using the in vivo MRI molecular-targeting approach.

Theodore Wagener, PhD

Department of Pediatrics, Section of General and Community Pediatrics, University of Oklahoma Health Sciences Center

Research Interests: 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 received his doctoral training in clinical psychology with a specialization in behavioral medicine and completed his clinical internship and T32 postdoctoral fellowship in cardiovascular behavioral medicine at Brown Medical School.

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.

Clinically, Dr. Wagener directs the Pediatric Behavioral Sleep Medicine Clinic at OU Children's Physicians where he treats children and adolescents with a variety of sleep disorders and also trains practicum students, interns, residents, and postdoctoral fellows in sleep medicine. Dr. Wagener is also involved with other Department of Pediatrics faculty members in training physicians and residents in the effective use of Motivational Interviewing for a variety of health behaviors.

Ashley Weedn, MD, MPH

Department of Pediatrics, Section of General and Community Pediatrics, University of Oklahoma Health Sciences Center

Research Interests: Ashley Weedn, MD, MPH (Principal Investigator) is a Board-certified pediatrician and Assistant Professor in the Department of Pediatrics, Section of General and Community Pediatrics. She graduated from Davidson College with a BA in Medical Ethics in 1998. She earned her medical degree from the University of Oklahoma College Of Medicine in 2005 and completed a pediatrics residency at Arkansas Children's Hospital in 2009. She returned to Oklahoma in 2010 to pursue a General Academic Pediatrics Fellowship, completed in 2012, during which she obtained a Masters in Public Health at OU College of Public Health.

Current clinical and research interests are in childhood obesity prevention. Specific research efforts have focused on the epidemiology of childhood obesity, initially in collaboration with the University of California San Francisco to determine the prevalence and trends of obesity in California children, which resulted in a platform presentation at the Pediatric Academic Societies Meeting and published in Pediatrics. More recent research endeavors have focused on determining measured prevalence of obesity in Oklahoma children and examining disparities in obesity among Oklahoma children, resulting in regional and national presentations and published in Clinical Pediatrics. Additional research interests include improving prevention and management of childhood obesity among primary care physicians and in community settings. Future research goals are to collaborate with Oklahoma Tribal Nations in order to develop strategies to identify, promote, and implement targeted interventions designed to reduce the childhood obesity epidemic in those at highest risk.

Aims of funded projects are to reduce disparities in obesity in Oklahoma children. Funding has been provided by the American Academy of Pediatrics to train pediatric residents in early childhood obesity prevention in Hispanic communities through collaboration with daycare centers. A NIH Loan Repayment Program was awarded with the project aim to examine obesity prevalence in low-income American Indian children participating in Tribal WIC programs.

Lauren A. Zenewicz, PhD

Department of Microbiology and Immunology, University of Oklahoma Health Sciences Center

Research Interests: Our research is primarily focused on interleukin-22 (IL-22), an important cytokine in the modulation of tissue responses during inflammation. IL-22 receptor expression is absent on immune cells, but is instead restricted to the tissues, providing signaling directionality from the immune system to the tissues. This molecule is highly upregulated in many chronic inflammatory diseases, including psoriasis, rheumatoid arthritis and inflammatory bowel disease (IBD). IL-22 is primarily made by activated lymphocytes, including T helper 17 (Th17) cells, natural killer (NK) cells and lymphoid tissue inducer (LTi)-like cells. Binding of IL-22 to its receptor on epithelial cells leads to activation of Stat3 and other signaling pathways. This induces proliferative and anti-apoptotic pathways, allowing for the maintenance of epithelial barriers as well as induction of many tissue-specific genes involved in inflammation. The role of IL-22 in inflammatory responses is complex and data suggest both pro- and anti-inflammatory functions.

Our studies examine the role of IL-22 in inflammation using mouse models of disease. Prior to our work, very limited data existed as to the functional role of IL-22 in vivo. We have shown that IL-22 plays a protective role in hepatitis (Immunity 2007) and inflammatory bowel disease (IBD) (Immunity2008). Our data suggest that IL-22 serves as a protective molecule to counteract the destructive nature of the immune response to limit tissue damage.

More recent work has exposed a pathogenic role for IL-22 in the inflamed colon using a newly developed experimental model of T cell-mediated colitis that is characterized by its slow progression, low IFNγ levels and thickening of the mucosal epithelium. We have shown that the intestinal pathology observed in this disease is associated with increased proliferation of colon epithelial cells, which was induced by IL-22 (JEM 2011). These data indicate that even within the same tissue the role of IL-22 during inflammation can be dual-natured and understanding this dichotomy is essential for the development of IL-22 based therapeutics. Our long-term goals are to gain a better understanding of the biology of IL-22 in health and disease.

Membership Program Information and Application

Peggy and Charles
STEPHENSON CANCER CENTER
at The University of Oklahoma

Membership Information

Mission and Overview

The mission of the Peggy and Charles Stephenson Cancer Center is to improve and extend the lives of cancer patients in Oklahoma through:

➢ Providing patient-centered, comprehensive care;
➢ Conducting innovative basic, translational and clinical research;
➢ Raising the level of cancer awareness and prevention among individuals and populations;
➢ Educating the next generation of cancer health care professionals; and
➢ Serving as a statewide resource for patients, researchers, health professionals and communities.

The Cancer Center advances this mission by promoting, coordinating and supporting cancer-focused research activities at the University of Oklahoma (OU) and research institutions in Oklahoma. Faculty who are actively engaged in cancer-focused research activities at OU or an Oklahoma research institution are eligible to be considered for membership in the Cancer Center and are encouraged to apply. All areas of cancer research are encouraged, including basic, translational, and clinical research, pharmaceutical sciences, population sciences, and the behavioral and psychosocial sciences.

Cancer Center Research Programs and Membership

Scientifically-focused, highly-collaborative research programs with active research members are essential attributes of National Cancer Institute (NCI)-designated cancer centers (and of academic cancer centers that seek to attain this designation). The NCI highlights the importance of these attributes in the guidelines for the Cancer Center Support Grant (P30):

> *"Cancer centers foster cancer-focused research, in part through the creation of formal scientific Programs. A Program comprises the activities of a group of investigators who share common scientific interests and goals and participate in competitively funded research. Programs should be highly interactive and lead to exchange of information, experimental techniques, and ideas that enhance the individual productivity of scientists and often result in collaborations and joint publications. Ultimately, the success of Programs is measured by scientific excellence and the emergence of productive collaborations. Selection of members of a center's Programs is one of the most critical decisions made by leadership. Functional and productive Programs select individuals for their scientific excellence and, just as importantly, for their commitment to work together to further the scientific goals of the cancer center."*

The Cancer Center has established a membership policy based on best practices from recently designated NCI cancer centers. The purpose of this policy is to define membership

responsibilities and benefits so that the Cancer Center can further its mission and goals of promoting, coordinating and supporting cancer-focused research activities at OU and other research institutions.

Responsibilities of Membership

All Cancer Center members are expected to actively participate in the Center through:

➢ Maintaining an active and cancer-focused research and / or clinical trials program
➢ Supporting research with peer-reviewed research funding
➢ Publishing research regularly in peer-reviewed journals
➢ Collaborating with other Cancer Center members to further Center research mission and goals
➢ Participating regularly in Cancer Center-sponsored seminars, program meetings, working groups and committees, retreats, etc.

In addition, all Cancer Center members are expected to:

➢ Submit all cancer-focused clinical research protocols to the Cancer Center Scientific Review Committee (SRC)
➢ Acknowledge the use of Cancer Center facilities, space and / or funding assistance, when appropriate, in research publications (standard acknowledgment text can be found on the Cancer Center website)
➢ Provide regular updates to the Cancer Center administration regarding publications, research support (including Notification of Grant Awards upon receipt), clinical protocols, patient accruals and / or other information that may be needed to fulfill the requirements of an NCI Cancer Center Support Grant application

Benefits of Membership

To promote and support cancer research the Cancer Center provides members with a number of benefits and support services:

➢ **Seed Grant Funding** – The Cancer Center annually issues RFPs to award seed grant funding to promising cancer-focused projects.

➢ **Research Program Membership** – As members of one of the Cancer Center's research programs you will have access to program activities intended to promote and support program-focused, collaborative research.

➢ **Clinical Trials Office** – Members receive support for developing and managing clinical trials from the regulatory, data management and clinical nursing cores in the Cancer Center's Clinical Trials Office.

➢ **Shared Resources** – The Cancer Center has multiple shared resources to support cancer research. Other shared resources will be added as the Center grows and demand can be demonstrated. Members will have prioritized access at a discounted rate.

➢ **NCI-Funded Research Incentive Funds** – Members who are PIs on qualifying NCI grants are eligible to receive a rebate of the equivalent of up to 10% of the incurred annual indirect costs, based on expenditures (for more information see the Cancer Center's "NCI- Funding Research Incentive Policy").

> **Distinguished Speaker Series and Research Seminars** – The Cancer Center annually hosts a Distinguished Speaker Series and Research Seminar Series for national and local speakers.

> **Proposal Services Support** – The Cancer Center has a proposal services core to help Cancer Center members with grant preparation and submission.

Membership Categories

The following categories and requirements were developed to ensure that the Cancer Center complies with the requirements of the NCI Cancer Center Support Grant:

Member
Researchers and clinicians with faculty appointments at OU or an affiliated research institution who are actively involved in cancer-focused research as evidenced by being 1) the primary or secondary author of peer-reviewed cancer-focused publications within the last three years and 2) a PI on a national, peer-reviewed, cancer-focused grant or contract within the last three years (from a sponsor recognized by the NCI) or a PI of a peer-reviewed, investigator-initiated, cancer-focused clinical trial within the last three years.

Some investigators new to the field of cancer research or junior investigators new to OU or an affiliated research institution may not meet the above criteria. However, such investigators can qualify for membership if they have a demonstrated interest in cancer and in securing national, peer-reviewed, cancer-focused research funding in the near future as determined by the Cancer Center Director (funding must be obtained within three years to maintain membership).
Faculty members who occupy senior leadership positions (Director, Deputy Director, Program Leaders and Core Leaders) within the Cancer Center qualify for membership.

Associate Member
Researchers and clinicians with faculty appointments at OU or an affiliated research institution who are engaged in cancer-focused research as evidenced by a record of publications and / or grants, but do not have national, peer-reviewed, cancer-related funding within the last three years.

Affiliate Member
Researchers and clinicians at an Oklahoma research institution who participate in cancer-related research and who demonstrate a commitment to the mission and goals of the Cancer Center.

Cancer Center Programs

Applicants are encouraged to select one of the following research programs that they believe best aligns with their primary research interests. An applicant may choose two programs (a primary and secondary) if he or she believes that their research interests are in multiple areas. If the programs below do not reflect an applicant's research, then please select "Non-Aligned."

The Cancer Center sponsors working groups in areas that may be of interest to Non-Aligned members.

Basic Cancer Biology Program

Program Leader: Ralf Janknecht, PhD

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.

Gastrointestinal Cancers Research Program
Program Leader: Courtney Houchen, MD

Researchers in the Gastrointestinal Cancers Research Program investigate the role that epithelial and mesenchymal stem cells play in the development, progression and metastasis of tumors of the gastrointestinal system, especially the colon, pancreas, liver, and esophagus. Another program goal is increasing the understanding of the role microRNAs play in tumor initiation. The program also focuses on the detection of plasma biomarkers for stem-cell related proteins in order to develop novel diagnostics for early cancer detection. Research in the Gastrointestinal Cancers Research Program includes laboratory-based basic, translational and preclinical research members in addition to an active clinical research program that encompasses phase I, II and III clinical trials.

Women's Cancers Research Program
Program Co-Leader: Scott McMeekin, MD
Program Co-Leader: Doris Benbrook, MD

The focus of the Women's 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 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 pill 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 programand focus groups.

Experimental Therapeutics Program
Program Director: Rajagopal Ramesh, PhD

The goal of the Experimental Therapeutics Program is to integrate novel therapies and technologies developed in the laboratory with clinical applications for treating human cancers.

The scientific aims of the program are 1) to develop and test novel, molecularly-targeted drugs, gene and drug delivery systems; 2) to develop and utilize in vitro and in vivo screening models; and to 3) identify molecular targets for new investigational drugs. Program members have expertise with the following: small molecule inhibitors; gene therapy (tumor suppressor genes, siRNA, mircro RNA, ncRNA, interleukins); drug delivery systems (polymers, dendrimers, nanomaterials, liposomes, viral vectors); chemistry (organic, medicinal, synthetic); animal models; photodynamic therapy; natural products; molecular imaging techniques and novel contrast agents; novel pharmacodynamic and pharmacokinetics analysis tools; and, 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.

Cancer Health Disparities Program
Program Leader: Mark Doescher, MD, MPH

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 underserved populations in the state.
- Engage underserved tribal and other underserved communities in collaborative cancer prevention and control research and strategies to reduce cancer-related health disparities.

Membership Application and Appointment Process

All interested faculty are encouraged to apply. A membership application form may be downloaded from the Cancer Center website for submission to the Office of Cancer Research.

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

The membership application process consists of two phases:

1) The Office of Cancer Research reviews all applications for completeness and forwards complete applications to the appropriate program leader(s).

2) The program leader(s) reviews the application and makes a recommendation concerning membership to the Cancer Center Director, who has final authority to assign membership.

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

Membership Review Process

The program leader(s) will review performance of program members at least once every three years. Based on this review, he / she will make recommendations concerning membership status to the Director. Members may be reassigned membership categories if criteria are not met.

To facilitate this review, 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.

The Cancer Center Director has final authority pertaining to membership assignment, reassignment and revocation.

Peggy and Charles
STEPHENSON CANCER CENTER
at The University of Oklahoma

Membership Application Form
(Please submit electronically)

Date of Application: _____

I. General Profile

Name (first, middle, last): _____
Degree(s): _____
Current Institution: _____
Faculty Appointment: _____
Admin Titles (if applicable): _____
Research Expertise: _____
Clinical Expertise (if applicable): _____
Campus address: _____
Telephone number: _____
Fax number: _____
Email address: _____

II. Category of Membership for which you are applying

☐ **Member (Full)**
Researchers and clinicians with faculty appointments at the University of Oklahoma or an affiliated research institution who are actively involved in cancer-focused research as evidenced by being 1) the primary or secondary author of peer-reviewed cancer-focused publications within the last three years and 2) a PI on a national, peer-reviewed, cancer-focused grant or contract within the last three years (from a sponsor recognized by the NCI) or a PI of a peer-reviewed, investigator-initiated, cancer-focused clinical trial within the last three years.

Some investigators new to the field of cancer research or junior investigators new to OU or an affiliated research institution will not meet the above criteria. However, such investigators can qualify for membership if they have a demonstrated interest in cancer and in securing national, peer-reviewed, cancer-focused research funding in the near future as determined by the Cancer Center Director (funding must be obtained within three years to maintain membership).

☐ **Associate Member**
Researchers and clinicians with faculty appointments at the University of Oklahoma or an affiliated research institution who are engaged in cancer-focused research as evidenced by a record of publications and / or grants,

but do not have national, peer-reviewed, cancer-related funding within the last three years.

☐ **Affiliate Member**
Researchers and clinicians at an Oklahoma research institution who participate in cancer-related research and who demonstrate a commitment to the mission and goals of the Stephenson Cancer Center.

III. <u>**Cancer Center Program for which you are applying**</u>
Applicants may choose two programs (a primary and secondary) if he or she believes that their research interests are in multiple areas.

___ Basic Cancer Biology Research Program

___ Gastrointestinal Cancers Research Program

___ Women's Cancer Research Program

___ Experimental Therapeutics Research Program

___ Cancer Health Disparities

___ Non-Aligned

Research program descriptions and a list of members can be found on the Peggy and Charles Stephenson Cancer Center website (www.OklahomaCancerCenter.org)

IV. <u>**Please briefly describe your current cancer-focused research**</u>

V. Please provide electronic copies of the following documents with your application form:

a) *Curriculum Vitae* (up-to-date)
b) NIH Biosketch (including an up-to-date list of publications)
c) Additional information you believe will assist in the evaluation of your application

Return via email to:

Peggy and Charles Stephenson Cancer Center
Office of Research
Phone: 405-271-1878
Email: CancerResearch@ouhsc.edu

All applicants will receive a letter from the Peggy and Charles Stephenson Cancer Center Director notifying them of membership status within 30 days of submitting a complete application.

Cancer Center Seed Grant Awardees

FY 2012 – FY 2013

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 Razaq, 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 / Cancer Health Disparities Research Program

Heather Basara, PhD	Health Information Improvement for the Chickasaw Nation
Valerie Eschiti, PhD RN	Perceived Barriers to HPV Vaccination by American Indian Youth and Caregivers
Elaine Hsieh, PhD	Medical Interpreters and Patient Communicative Competence in Gynecological Oncology
Paul Spicer, PhD	Children's Environment and Obesity in an American Indian Community

TSET Cancer Research Program Research Support / Experimental Therapeutics Research Program

Anupama Munshi, PhD	Urolithin, metabolite of pomegranate juice, as a chemopreventive agent for breast cancer
Sukyung Woo, PhD	Effective translation of *in vitro* synergistic combination into maximal *in vivo* synergy

Doris Benbrook, PhD and Franklin Hays, PhD	Therapeutic Targeting of HSP70 Chaperones in Cancer Drug Discovery

TSET Cancer Research Program Research Support / Women's Cancers Research Program

Doris Benbrook, PhD and Christopher West, PhD	Glycoprotein Analysis of Gynecological Cancers
Sukyung Woo, PhD	Phase 0 Trial of NSC 726189 (SHetA2) in patients with dysplasia
Doris Benbrook, PhD, Rajagopal Ramesh, PhD, Marie Hanigan, PhD	Ovarian Cancer Chemoresistance Subgroup
Jay Hanas, PhD	Uterine Cancer Study
Erin Bishop, MD	CCLD Cytokine in Co-Morbiditites of Endometrial Cancer, Diabetes and Obesity

TSET Cancer Research Program Research Support / Basic Cancer Biology Research Program

Blaine Mooers, PhD	Structural Studies of Human JMJD4 by X-ray Methods
Joe Zhao, PhD	The Role of p53 in JAK2V617F-Induced Myeloproliferative Neoplasms

TSET Cancer Research Program Research Support / Supportive Care and Outcomes Research Working Group Pilot Studies

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

University of Oklahoma Bioengineering Center / TSET Cancer Research Program Research Support

Ralf Janknecht, PhD and Vassilios Sikavitsas, PhD	3D Model for prostate cancer metastasis and the role of KDM4 histone demthylaes 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 Cancers

Evaluation Form

Evaluation Form

SCC Cancer Research Symposium
March 29, 2013

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.