2020 ANNUAL
CANCER RESEARCH SYMPOSIUM

Friday | Feb. 7 | 2020

Stephenson
CANCER CENTER
The UNIVERSITY *of* OKLAHOMA

A NATIONAL CANCER INSTITUTE DESIGNATED CANCER CENTER

OU Medicine

HOSTED BY STEPHENSON CANCER CENTER

NCI Cancer Center

A Cancer Center Designated by the
National Cancer Institute

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NATIONAL
CANCER
2019-20

TSET

The Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Settlement Endowment Trust (TSET) for co-sponsoring the 2020 Stephenson Cancer Research Symposium.

In 2012 TSET awarded a five-year, $30.25 million grant to the Stephenson Cancer Center to establish the Oklahoma TSET Cancer Research Program. In 2017 TSET renewed this award for an additional five year period.

The mission of the Oklahoma TSET Cancer Research Program is to decrease the burden of cancer in Oklahoma and nationally through promoting, coordinating and supporting innovative cancer research. It seeks to accomplish this mission through:

- Attracting cancer researchers with grant funding from the National Cancer Institute and other national sponsors to Oklahoma
- Developing trans-disciplinary, collaborative cancer research programs
- Promoting inter-institutional partnerships to leverage unique strengths at research institutions in Oklahoma
- Enhancing research infrastructure and shared resources to enable and support innovative and nationally-competitive cancer research
- Serving as a statewide resource for researchers and institutions that conduct cancer research

The Oklahoma TSET Cancer Research Program supports a wide range of programs, shared resources and initiatives designed to accomplish these goals.

Five Year Highlights

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

- Increased cancer center membership from 75 to 279 members at nine academic institutions across Oklahoma
- Recruited forty three new cancer researchers to Oklahoma
- Funded over fifty seed and directed-research grants to cancer investigators in Oklahoma
- Enhanced five Shared Resource facilities
- Hosted over 300 research seminar speakers
- Hosted annual statewide Cancer Research Symposium that brings together over 250 researchers from around the state
- Hosted over 60 undergraduate students from 26 different universities for a summer cancer research experience
- Opened 627 new cancer clinical trials
- Enrolled 4114 patients to interventional clinical trials
- Enrolled 5089 patients to non-interventional clinical trials
- Opened 114 new Phase I and Phase I/II clinical trials
- Enrolled 786 patients to Phase I clinical trials

OTRC
OKLAHOMA TOBACCO
RESEARCH CENTER

Stephenson Cancer Center wishes to recognize and thank the
Oklahoma Tobacco Research Center (OTRC)
for co-sponsoring the 2020 Stephenson Cancer Research Symposium.

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The mission of the Oklahoma Tobacco Research Center (OTRC) is to reduce, and ultimately eliminate, tobacco- related morbidity and mortality in Oklahoma through research that informs interventions and policies with a particular emphasis on addressing tobacco-related health disparities.

The following goals help drive our mission:

1. To be a leading tobacco research program with a focus on the entire translational continuum – from the discovery of basic mechanisms of tobacco use, cessation, and relapse, to the development and evaluation of novel tobacco treatments, to the dissemination and implementation of treatments, policies, and education throughout Oklahoma.
2. To effectively and efficiently deliver state-of-the- science, evidence-based tobacco treatment to Oklahomans throughout the State.
3. To train the next generation of tobacco researchers.

In addition, the OTRC provides tobacco cessation services across the state through its Tobacco Treatment Research Program.

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

OTRC Directors & Faculty
Michael S. Businelle, PhD (Director)
Darla E. Kendzor, PhD (Director)
Than C. Bui, MD, DrPh
Amy Cohn, PhD
Summer Frank-Pearce, PhD
Emily T. Hébert, DrPH
Ce Shang, PhD
Alayna P. Tackett, PhD

TSET

2020 ANNUAL

CANCER RESEARCH

SYMPOSIUM

10:00 – 10:30	**Registration & Poster Check-In** Samis Level 2
10:30 – 12:00	**Lunch & Poster Session** Samis Levels 1 & 2
12:00 – 12:15	**Welcome & State of the Cancer Center** Samis Auditorium
12:15 – 1:15	**Keynote Address** Samis Auditorium
1:30 – 2:30	**Session I** Cancer Biology – Samis Auditorium Cancer Prevention & Control – Samis Basement Cancer Therapeutics – Andrews Academic Tower A & B
2:30 – 3:30	**Session II** Cancer Biology – Samis Auditorium Cancer Prevention & Control – Samis Basement Cancer Therapeutics – Andrews Academic Tower A & B
3:30 – 3:45	**Break – snacks provided**
3:45 – 4:45	**Session III** Cancer Biology – Samis Auditorium Cancer Prevention & Control – Samis Basement Cancer Therapeutics – Andrews Academic Tower A & B
4:45 – 5:00	**Break**
5:00 – 5:15	**Awards & Closing Remarks** Samis Auditorium
5:15 – 6:15	**Reception** Samis Level 1

SCHEDULE AT A GLANCE

2020 ANNUAL

CANCER RESEARCH
SYMPOSIUM

10:00 – 10:30	**Registration & Poster Check-In**
10:30 – 12:00	**Lunch & Poster Session** Samis Level 1 & 2
12:00 – 12:15	**Welcome & State of the Cancer Center** Samis Auditorium Mark Doescher, MD
12:15 – 1:15	**Keynote Address** Samis Auditorium Anil Sood, MD
1:30 – 2:30	**Session I**

Cancer Biology Track – Samis Auditorium
Moderators: Arlan Richardson & Marie Hanigan

INTRODUCTION & PROGRAM UPDATES
Min Li

CROSSTALK BETWEEN GROWTH FACTOR SIGNALING AND THE ESTROGEN RECEPTOR IN A PRECLINICAL MODEL OF OBESITY AND BREAST CANCER
Elizabeth Wellberg

XRN2 MEDIATES DNA DOUBLE STRAND BREAK REPAIR THROUGH RNA: DNA HYBRID RESOLUTION
Julio Cesar Morales

DEVELOPMENT OF A MODEL OF DIHOMO-GAMMA-LINOLENIC ACID INTERFERENCE WITH PLATELET PROMOTION OF OVARIAN CANCER
Zitha Redempta Isingizwe

DETAILED AGENDA

2020 ANNUAL
CANCER RESEARCH
SYMPOSIUM

Cancer Prevention & Control Track – Samis Basement
Moderator: Amy Cohn

YOUTH USE OF E-CIGARETTES IN THE UNITED STATES: DIFFERENCES IN USER CHARACTERISTICS BY DEVICE TYPE
Alayna Tackett

ELECTRONIC CIGARETTES AS A HARM REDUCTION STRATEGY: A DNA DAMAGE PERSPECTIVE
Lurdes Queimado

ASSESSING COGNITIVE AND EMOTIONAL PROCESSING OF RISK ANTI-HOOKAH MESSAGES AMONG YOUNG ADULTS
Glenn Leshner

Panel Q&A

Cancer Therapeutics Track – Andrews Academic Tower A & B
Moderator: Kathleen Moore

ACIDIC TUMOR MICROENVIRONMENT TARGETED NANOPARTICLES FOR THE DETECTION OF TRIPLE-NEGATIVE BREAST CANCER BY MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY
Abhilash Samykutty

GAIT SPEED CHANGE IN FIRST CHEMOTHERAPY CYCLE MAY PREDICT LATER DOSE-REDUCTION IN EXPLORATORY ANALYSIS OF OVARIAN CANCER PATIENTS OVER 70
Anjalika Gandhi

DETAILED AGENDA

OUTCOMES OF EARLY STAGE ENDOMETRIAL CANCER IN MEDICALLY COMPLEX WOMEN; HORMONAL CONTROL COMPARED TO TRANSVAGINAL HYSTERECTOMY
Christina Washington

SINGLE CELL RNA SEQUENCING DELINEATES ACTIVATION OF INNATE AND ADAPTIVE IMMUNE CELLS BY A LOCAL PHOTO-IMMUNOTHERAPY FOR TREATMENT OF METASTATIC MAMMARY TUMORS
Wei Chen

2:30 – 3:30   **Session II**

Cancer Biology Track – Samis Auditorium
Moderators: Ralf Janknecht & Mark Lang

DIFFERENTIAL EXPRESSION OF INFLAMMATORY MARKERS AND ASSOCIATION WITH GENDER IN HEPATITIS C-RELATED CIRRHOSIS AND HEPATOCELLULAR CARCINOMA
Sarah Groover

ELUCIDATING THE ROLE OF TRAF7 IN MENINGIOMA DEVELOPMENT
Panayiotis Pelargos

ELUCIDATING THE ROLE OF XRN2 IN GLIOBLASTOMA MULTIFORME INVASION
Tuyen Dang

TRANSCRIPTIONAL ACTIVATION OF A NOVEL ZEB1-INTEGRIN-ENT1 SIGNALING UNDERLIES THE ROLE OF ZINC TRANSPORTER ZIP4 IN PANCREATIC CANCER CHEMORESISTANCE
Mingyang Liu

DETAILED AGENDA

Cancer Prevention & Control Track – Samis Basement
Moderators: Darla Kendzor & Michael Businelle

A PILOT RANDOMIZED CONTROLLED TRIAL OF A MOBILE JUST-IN-TIME ADAPTIVE INTERVENTION FOR SMOKING CESSATION
Emily Hébert

DARKER SKIN COLOR IS ASSOCIATED WITH A LOWER LIKELIHOOD OF SMOKING CESSATION AMONG MALES BUT NOT FEMALES
Adam Alexander

DAILY REPORTS OF SLEEP AND SMOKING ABSTINENCE: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY
Karen Ra

Panel Q&A

Cancer Therapeutics Track – Andrews Academic Tower A & B
Moderator: Kathleen Moore

LASER IMMUNOTHERAPY REQUIRES TYPE I IFNS IN THE TREATMENT OF METASTATIC B16 MELANOMA IN MICE
Ashley Hoover

IMPACT OF SOCIAL SERVICES ON DEPRESSION AND TREATMENT OUTCOMES AMONGST WOMEN WITH LOCALLY ADVANCED CERVIX CANCER
Elizabeth Evans

NOVEL OVARIAN CANCER MAINTENANCE THERAPY TARGETED AT MORTALIN AND MUTANT P53
Satish Kumar Ramraj

PHASE II TRIAL OF VAGINAL CUFF BRACHYTHERAPY FOLLOWED BY DOSE-DENSE CHEMOTHERAPY IN EARLY STAGE ENDOMETRIAL CANCER PATIENTS WITH ENRICHED, HIGH-INTERMEDIATE RISK FACTORS FOR RECURRENCE
Tara Castellano

3:30 – 3:45   **Break – snacks provided**

3:45 – 4:45   **Session III**

Cancer Biology Track – Samis Auditorium
Moderators: Jie Wu & Jingxuan Yang

SEXUAL DIMORPHISMS WITHIN THE TUMOR MICROENVIRONMENT OF COLORECTAL CANCER
Andrea Geddes

FOCAL ADHERENT KINASE (FAK) IS A VULNERABILITY OF RESIDUAL FIBROTIC STOMA IN THE TRANSGENIC MOUSE MODEL OF KIF5-RET-INDUCED LUNG TUMORS
Xuan Liu

MPS1 EXPRESSION IS CRITICAL FOR CHROMOSOME ORIENTATION AND SEGREGATION IN YEAST WITH HIGH PLOIDY
Regis Meyer

MODELING ACUTE LYMPHOBLASTIC LEUKEMIA IN ZEBRAFISH WITH TRANSGENIC HUMAN MYC
Gilseung Park

DETAILED AGENDA

2020 ANNUAL

CANCER RESEARCH

SYMPOSIUM

Cancer Prevention & Control Track – Samis Basement
Moderator: Paul Spicer

COLORECTAL CANCER AND SCREENING ACROSS AMERICAN INDIAN COMMUNITIES
Dorothy Rhoades
BREAST CANCER SURVIVORS' POSTURAL SWAY EXCEEDS EXPECTATIONS FOR AGE OR VESTIBULAR PATHOLOGY: A CROSS–SECTIONAL ANALYSIS
Elizabeth Hile

Panel Q&A

Cancer Therapeutics Track – Andrews Academic Tower A & B
Moderator: Kathleen Moore

INHIBITION OF GRANULOCYTE COLONY STIMULATING FACTOR EXTENDS SURVIVAL IN AN ADVANCED MODEL OF METASTATIC COLORECTAL CANCER VIA INCREASED ANTI-TUMOR IMMUNE EFFECTS
Anita Ray

A GLOBAL RNA INTERFERENCE MECHANISM FOR THE TREATMENT OF PROSTATE CANCER
Maria Ruiz-Echevarria

ASSESSMENT OF A SCFV ANTIBODY FRAGMENT AGAINST ELTD1 IN A G55 GLIOBLASTOMA XENOGRAFT MODEL USING A MOLECULAR TARGETING APPROACH
Michelle Zalles

ONC201, A TRAIL INDUCING SMALL MOLECULE, PREVENTS INTESTINAL TUMORS IN FAP MOUSE MODEL
Venkateshwar Madka

4:45 – 5:00   **Break**

DETAILED AGENDA

2020 ANNUAL
CANCER RESEARCH
SYMPOSIUM

5:00 – 5:15   **Awards & Closing Remarks**
Samis Auditorium

5:15 – 6:15   **Reception**
Samis Level 1

DETAILED AGENDA

Anil K. Sood, M.D.
Professor and Vice Chair for Translational Research
Departments of Gynecologic Oncology and Cancer Biology
Co-director of the Center for RNA Interference and Non-Coding RNA
The University of Texas MD Anderson Cancer Center

Dr. Anil K. Sood is Professor in the Department of Gynecologic Oncology and Reproductive Medicine at the UT MD Anderson Cancer Center. He holds a joint appointment in Cancer Biology and is co-director of the Center for RNA Interference and Non-Coding RNA at the M. D. Anderson Cancer Center. He is also Director of the multi-disciplinary Blanton-Davis Ovarian Cancer Research Program and co-leads the Ovarian Cancer Moonshot Program.

Dr. Sood received his medical degree from the University of North Carolina, Chapel Hill. A major and consistent theme of his scientific research has been on understanding human cancer biology and converting lab discoveries into novel therapeutics. His research group has made several seminal research contributions in the fields of tumor microenvironment, nanomedicine, and neuroendocrine effects on cancer biology. Dr. Sood has received recognition for his research accomplishments including the Hunter Award, the Margaret Greenfield/Carmel Cohen Excellence in Ovarian Cancer Research Prize, and the GCF/Claudia Cohen Research Foundation Prize for Outstanding Gynecologic Cancer Researcher. He is an elected member of the American Society for Clinical Investigation (ASCI), the American Association for the Advancement of Science (AAAS), and the Association of American Physicians (AAP). Dr. Sood was selected as an American Cancer Society Research Professor in 2017.

KEYNOTE SPEAKER
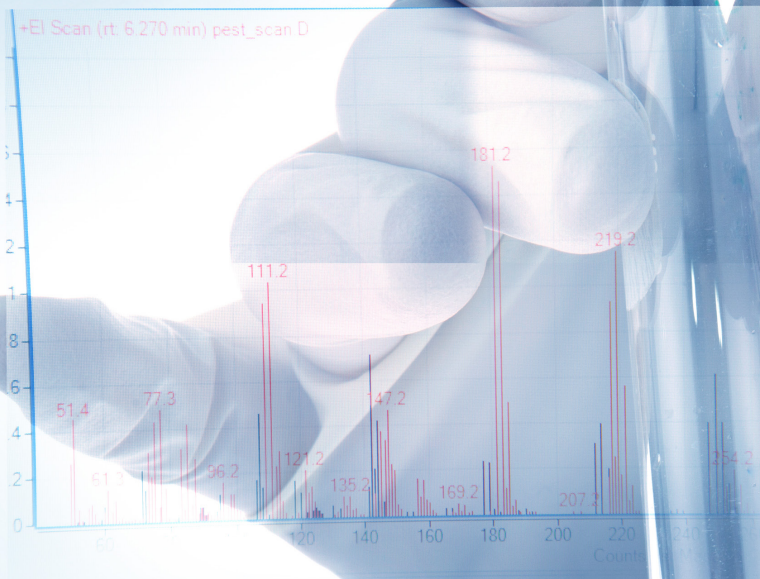
CANCER BIOLOGY

1:30 – 2:30 PM   ## SESSION I
                          Moderator: Arlan Richardson & Marie Hanigan

1:30 – 1:44 PM   **INTRODUCTION**
                          Min Li, PhD

1:45 – 1:59 PM   **CROSSTALK BETWEEN GROWTH FACTOR SIGNALING AND THE ESTROGEN RECEPTOR IN A PRECLINICAL MODEL OF OBESITY AND BREAST CANCER**
                          Elizabeth Wellberg, PhD
                          Department of Pathology
                          University of Colorado Anschutz Medical Campus

2:00 – 1:14 PM   **XRN2 MEDIATES DNA DOUBLE STRAND BREAK REPAIR THROUGH RNA: DNA HYBRID RESOLUTION.**
                          Julio Cesar Morales, PhD
                          Department of Neurosurgery
                          University of Oklahoma College of Medicine

2:15 – 2:29 PM   **DEVELOPMENT OF A MODEL OF DIHOMO-GAMMA-LINOLENIC ACID INTERFERENCE WITH PLATELET PROMOTION OF OVARIAN CANCER**
                          Zitha Redempta Isingizwe
                          Department of Pharmaceutical Sciences
                          University of Oklahoma Health Sciences Center

2:30 – 3:30 PM   ## SESSION II
                          Moderator: Ralf Janknecht and Mark Lang

2:30 – -2:44 PM   **DIFFERENTIAL EXPRESSION OF INFLAMMATORY MARKERS AND ASSOCIATION WITH GENDER IN HEPATITIS C-RELATED CIRRHOSIS AND HEPATOCELLULAR CARCINOMA**
                          Sarah Groover
                          Departments of Biochemistry and Microbiology
                          University of Oklahoma Health Sciences Center

2:45 – 2:59 PM   **ELUCIDATING THE ROLE OF TRAF7 IN MENINGIOMA DEVELOPMENT**
                          Panayiotis Pelargos, MD
                          Department of Neurosurgery
                          University of Oklahoma Health Sciences Center

3:00 – 3:14PM   **ELUCIDATING THE ROLE OF XRN2 IN GLIOBLASTOMA MULTIFORME INVASION**
                          Tuyen Dang, PhD
                          Department of Neurosurgery
                          University of Oklahoma Health Sciences Center

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                          Mingyang Liu, PhD
                          Department of Internal Medicine
                          University of Oklahoma Health Sciences Center

3:45 – 4:45 PM   SESSION III
Moderator: Jerry Wu and Jingxuan Yang

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Andrea Geddes, MD
Department of Surgery
University of Oklahoma Health Sciences Center

4:00 – 4:14 PM   **FOCAL ADHERENT KINASE (FAK) IS A VULNERABILITY OF RESIDUAL FIBROTIC STOMA IN THE TRANSGENIC MOUSE MODEL OF KIF5-RET-INDUCED LUNG TUMORS**
Xuan Liu, PhD
Department of Pathology
University of Oklahoma Health Sciences Center

4:15 – 4:29 PM   **MPS1 EXPRESSION IS CRITICAL FOR CHROMOSOME ORIENTATION AND SEGREGATION IN YEAST WITH HIGH PLOIDY**
Regis Meyer, PhD
Departments of Cell Biology
University of Oklahoma Health Sciences Center

4:30 – 4:44 PM   **MODELING ACUTE LYMPHOBLASTIC LEUKEMIA IN ZEBRAFISH WITH TRANSGENIC HUMAN MYC**
Gilseung Park, MD, PhD
Department of Cell Biology
University of Oklahoma Health Sciences Center

CROSSTALK BETWEEN GROWTH FACTOR SIGNALING AND THE ESTROGEN RECEPTOR IN A PRECLINICAL MODEL OF OBESITY AND BREAST CANCER

Elizabeth A Wellberg1, Peter Kabos2, Stevi J Johnson1, Fotobari V Kinanee1, Austin E Gillen3, Susan M Edgerton1, Ann D Thor1, Carol A Sartorius1, Paul S MacLean4
1Department of Pathology; 2Division of Medical Oncology, 3RNA Biosciences Program, 4Division of Endocrinology, Metabolism, & Diabetes, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado
Elizabeth.wellberg@cuanschutz.edu

Introduction: Obesity increases the risk and worsens prognosis for breast cancer. The majority of breast tumors are diagnosed in postmenopausal women and express the estrogen receptor (ER). Epidemiological studies suggest that adult weight gain and insulin resistance underlie the detrimental effect of obesity on breast cancer. While significant advances have been made in understanding the impact of obesity on breast cancer biology, there are no preclinical models that incorporate excess adiposity, weight gain, insulin resistance, and ER-positive breast tumors, which represents a gap in our ability to study this disease.

Objective and Methods: Our goal was to develop a murine model of obesity that could be combined with ER-positive breast cancer patient xenografts (PDX). We used a high fat (45%)/high sucrose (HF) diet to promote body fat gain in immune-compromised female Rag1-null C57Bl/6 mice. Lean mice were maintained on low fat (11%)/no sucrose (LF), and all mice were housed at thermoneutrality (~30C) to reduce the chronic cold stress that mice experience at standard room temperature and to promote fat accumulation. Mature females were ovariectomized, supplemented with estradiol (E2), and grafted with ER-positive human breast cancer cells (MCF7) or a novel PDX developed at the University of Colorado (UCD12). When tumors reached a defined volume, mice were randomized based on body fat percentage within diet groups to receive E2-maintenance, or estrogen withdrawal (EWD) to model postmenopausal breast cancer therapy. The study was terminated 3 weeks after treatment, at which point adipose, blood, and tumor tissues were evaluated.

Results: After EWD, only HF mice gained weight and developed insulin resistance. Despite this, MCF7 tumors regressed in both LF and HF groups. In contrast, the UCD12 tumors continued to grow in HF but not LF mice. These ER-positive tumors represented responders (MCF7) and non-responders (UCD12) to EWD in the context of obesity. An unbiased screen of tumor tissue revealed that fibroblast growth factor receptor 1 (FGFR1) was activated in UCD12 tumors from HF females after EWD. Analysis of adjacent adipose tissue demonstrated that the fibroblast growth factor 1 (FGF1) ligand was produced specifically in HF mice, and increased with weight gain, suggesting ligand-dependent activation of FGFR1 in tumors. Inhibition of FGFR restored sensitivity to EWD in HF mice. Mechanistic studies in cultured cells indicated that FGF1 increased phosphorylation of ER only in UCD12, but not MCF7 cells.

Conclusions: FGFR1 may be activated in a subset of ER-positive breast cancers in the context of obesity, weight gain, and insulin resistance. Crosstalk between FGFR1 and ER may help maintain ER activity after EWD. Current studies are focused on identifying variables that dictate when FGFR1 can activate ER in breast cancer cells, and whether this pathway may allow the tumor to retain dependence on ER after therapy in the obese environment, even when estrogen has been removed.

XRN2 MEDIATES DNA DOUBLE STRAND BREAK REPAIR THROUGH RNA: DNA HYBRID RESOLUTION

Julio Morales

There is a growing body of evidence that demonstrates a connection between factors traditionally associated with transcription and the double strand break (DSB) repair pathways. During the process of normal transcription RNA: DNA hybrids (R loops) are formed and resolved, causing no harm to the cell. However, unresolved R loops have been associated with DSB formation, genetic instability, and chromosomal translocations. This genetic instability primarily occurs in S-phase, where the replication machinery collides with unresolved R loops. These collisions lead to DSB formation, chromosomal translocations, and eventually tumors; due to the inherent oncogenic potential of free DNA ends. Interestingly, it has been demonstrated that R loops are required to be made and resolved in a timely manner at the break site for DNA repair to be completed effectively. How the cell deals with these R loops made in response to DSB formation is not known. One factor that bridges the DNA repair and transcription fields is the 5'-3' exoribonuclease XRN2. We have gathered data implicating XRN2 in the response and repair of DSBs. We found that loss of XRN2 leads to increased DSB formation, sensitivity to ionizing radiation, replication stress and R-loop formation. We also found that there is an accumulation of DSB repair factors at the poly-A region of genes that undergo R-loop dependent transcription termination. Using a plasmid based non-homologous end-joining (NHEJ) assay, we found that loss of XRN2 abrogates the cells ability to repair DNA via the NHEJ pathway. Yet, the mechanistic function of XRN2 in the NHEJ repair pathway is not known. Loss of XRN2 leads to an increase in R loops at the poly-A region of the β-actin gene. We can demonstrate that H2AX is phosphorylated at this region of the genome with XRN2, suggesting the loss of XRN2 is leading to DSB formation. Interestingly, loss of XRN2 also leads to a decrease Ku70 accumulation at the poly-A region of the β-actin gene. Also, we have found that over-expression of human RNaseH1, an enzyme that specifically degrades RNA moieties from RNA: DNA hybrids, restores Ku70 binding to the poly-A region of the β-actin gene after loss of XRN2. These data suggest that the mechanistic function of XRN2 in NHEJ to aid in resolving R loops formed at the DSB site, allowing Ku70 binding and NHEJ repair pathway progression.

DEVELOPMENT OF A MODEL OF DIHOMO-GAMMA-LINOLENIC ACID INTERFERENCE WITH PLATELET PROMOTION OF OVARIAN CANCER

Zitha Redempta Isingizwe[1] and Doris M. Benbrook[1,2]

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[1]Departement of Pharmaceutical Sciences, University of Oklahoma Health Sciences Center
[2]Departement of Obstetrics and Gynecology, Gynecologic Cancer Program, Stephenson Cancer Center

Background: Cancer is the second leading cause of deaths worldwide after cardiovascular diseases. A commonality between cancer and cardiovascular diseases is disregulation of platelets. Platelets and cancer are known to promote each other in a feedforward mechanism that is poorly understood. A long chain polyunsaturated fatty acids dihomo-gamma-linolenic acid (DGLA) was shown to reduce cardiovascular events in a platelet dependent manner while the exact mechanism of DGLA-mediated cancer cells death is yet to be explored.

Objectives: The objective of our study was to develop an experimental model to study interventions that could disrupt the cancer/platelets loop.

Methods: The effects of a range of DGLA concentrations on platelet aggregation and growth of high-grade serous ovarian cancer cell lines (OVCAR3, MesOV, OVSAHO), normal human fallopian tube secretory epithelial cells (hFTSECs) primary culture and an immortalized hFTSEC cultures were determined with an MTT assay. Cocultures were used to evaluate effects of platelets on ovarian cancer cell line spheroid formation and size and effects of ovarian cancer cells and hFTSECs on platelet aggregation.

Results: The minimal cytotoxic DGLA concentrations for cancer and normal epithelial cells were above physiologically-achievable concentrations, and the half maximal inhibitory concentrations (IC50's) were similar across epithelial cell types with the IC50's for hFTSEC primary culture (261 μM) and immortalized culture (206 μM) falling within the range of cancer cell IC50's (153-275 μM). DGLA inhibited platelet aggregation at concentrations ≥250 μM. Platelets increased cancer spheroid sizes in a concentration-dependent manner and cancer cells, but not hFTSECs, induced platelet aggregation in cocultures.

Conclusions: Our model incorporates both platelet effects on cancer cells and cancer cell effects on platelets. Physiologically-achievable DGLA concentrations that affect platelet aggregation without affecting epithelial cells were identified. Minimal doses of DGLA needed to cause cytotoxicity against cancer and normal cells are above levels that are physiologically achievable.

Future Directions: Future studies will utilize DGLA doses that can interfere with platelet aggregation without directly causing cytotoxicity to cancer or healthy cells. This experimental model will allow study of DGLA's potential for interfering with platelet promotion of ovarian cancer in the absence of direct effects of DGLA on cancer cells.

DIFFERENTIAL EXPRESSION OF INFLAMMATORY MARKERS AND ASSOCIATION WITH GENDER IN HEPATITIS C-RELATED CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

Sarah Groover,[1] Savannah Nicks,[1] Amy Yuhan Brooks,[1] Mitchelle Wanjiku Mwangi,[1] Riley Pritzlaff,[1] Anil Kaul,[2] and Rashmi Kaul[1]

[1]Department of Biochemistry and Microbiology, and [2]School of Health Care Administration, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA

Correspondence to: sgroove@okstate.edu

Hepatocellular carcinoma (HCC) is a leading cause of cancer death in the world and is strongly linked to chronic liver disease and cirrhosis. Hepatitis C virus (HCV)-related cirrhosis is the prime cause of rising incidence of HCC in developed countries including the United States. Clinical observations have established gender-based differences in HCV infection with the disease progressing more rapidly in males and postmenopausal females. In contrast, premenopausal women with circulating estrogen have been associated with less severity and slower progression through all stages of HCV infection. We recently reported gender differences in estrogen receptor (ER) subtype expression in normal livers and increased ER subtype expression in HCV pathogenesis, suggesting that estrogens and their receptors may play an important role in hepatic defenses and development of HCV-mediated cirrhosis and HCC. The precise mechanism of estrogen protection in premenopausal females and worse prognosis in males and postmenopausal females is poorly understood. Since HCV disease pathogenesis depends largely on chronic inflammation, in the present study we hypothesized that ERs in the liver interact with innate inflammatory markers such as TNFα, IL-33, and CD55 to cause cirrhosis and HCC development.

We analyzed the mRNA gene expression of ESR1, ESR2, TNFα, IL-33, and CD55 in liver tissues using quantitative PCR in patients with either HCV-related cirrhosis (N = 32) or HCV-related HCC (N = 23) and compared to healthy samples with no HCV or HCC diagnosis (N = 38). Our results indicate that in patients with HCV-related HCC, ESR2 expression is decreased (p = 0.020) while the ratio of ESR1:ESR2 expression is increased (p = 0.025). TNFα is significantly increased in both HCV-related cirrhosis (p = 0.00025) and HCC (p = 0.0031). Interestingly, Spearman's correlations indicate a strong negative correlation between ESR1 and ESR2 expression among females with HCV-related cirrhosis (rs = -0.84, p = 0.0002) and a positive correlation among males (rs = 0.57, p = 0.020). We also found a positive correlation between ESR2 and TNFα expression in both males with HCV-related cirrhosis (rs = 0.58, p = 0.016) and females (rs = 0.64, p = 0.012), as well as in males with HCV-related HCC (rs = 0.60, p = 0.0083).

We conclude that the expression levels of ESR2 observed in HCV-related cirrhosis and HCC may regulate HCV-associated inflammation and disease progression, particularly the differential interactions of ESR2 and ESR1 between males and females. The association of ESR2 with TNFα in HCV-related cirrhosis and HCC may have some significance and needs further investigation.

ELUCIDATING THE ROLE OF TRAF7 IN MENINGIOMA DEVELOPMENT

Panayiotis E. Pelargos, Erdyni N. Tsistikov, Alla Tsytsykova, Ian F. Dunn
Oklahoma University Health Sciences Center, Department of Neurosurgery
panayiotis-pelargos@ouhsc.edu

Meningiomas are the most common primary intracranial neoplasm in adults, accounting for over one-third of all primary central nervous system (CNS) tumors with annual incidence of approximately 30,000 new cases. Analyses of sporadic meningiomas identified inactivating mutations or copy loss of the 22q region harboring the Neurofibromin 2 (NF2) gene in 40–60% of cases. Besides NF2, our group and others identified a number of several additional genes with mutations using next-generation sequencing. These include AKT1, KLF4, TRAF7, SMO, and others. Missense mutations in TRAF7 (TNF Receptor-Associated Factor 7) were exclusive of NF2 inactivation and occur in ~28% of meningiomas. The majority of meningiomas with TRAF7 mutations also contain mutations in either AKT1 or KLF4.

Little is known as to how the TRAF7 gene product contributes to tumorigenesis. There are seven known mammalian TRAF proteins that share a particular modular domain organization. With the exception of TRAF1, all TRAF proteins contain a RING (Really Interesting New Gene) domain at the N terminus. The RING proteins are thought to be E3 ubiquitin ligases which participate in the attachment of ubiquitin, a small regulatory protein found in most tissues of eukaryotic organisms, to other proteins. Ubiquitination is mediated by the sequential action of an E1 activating enzyme (2 per genome), an E2 conjugating enzyme (~40 per genome), and a range of E3 proteins (more than 600), which are thought to confer substrate specificity.

Previous analysis of the high-density human E2/E3-RING network using yeast two-hybrid (Y2H) screens combined with true homology modeling methods has revealed complex combinatorial interactions and demonstrated that TRAF7 weakly interacts with several E2 proteins and strongly binds to E2L6. We were not able to reproduce these results by using a Y2H system available in our lab. To examine whether TRAF7 binds with any other protein/s, we screened a normalized universal human cDNA library using our system. The analysis revealed several TRAF7-interacting proteins; the most frequently found was Copper Metabolism Murr1 Domain-containing protein 10 (COMMD10). These results were in agreement with recently published data where TRAF7 was identified as a COMMD10-binding protein by using high-throughput affinity-purification mass spectrometry. The resulting network (BioPlex) contained contains 23,744 interactions among 7,668 proteins.

All ten members of COMMD family are ubiquitously expressed and share a structurally conserved C-terminal motif, the COMM domain, which in case of COMMD10 appears to interact with TRAF7. Recent studies in human cells revealed that COMMD proteins are essential components of the COMMD1-10/CCDC22/CCDC93 protein complex, dubbed "Commander". Commander likely plays a fundamental cellular function and is critical for vertebrate embryogenesis. Defects in the complex and its interaction partners disrupt heart, brain, and craniofacial development. Previous studies have shown that COMMD10 is important for activation of transcription factor EB (TFEB), a master inducer of lysosomal biogenesis, and associated phagolysosome maturation. Therefore, TRAF7's interaction with COMMD10 may play a key role in meningioma and tumor development in general and determination of that role stands to provide insight into the mechanisms of tumor development.

ELUCIDATING THE ROLE OF XRN2 IN GLIOBLASTOMA MULTIFORME INVASION

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Glioblastoma multiforme (GBM) is a highly aggressive brain cancer. The standard course of treatment is a combination of radiation and chemotherapy. Even with the dual treatment, the 5-year survival rate of patients with GBM is between 4-7%. Therefore, there is an urgent need to develop novel therapies to increase the survivorship. A possible cause of the low survival rate for GBM patients is the presence of motile neoplastic cells. These motile cells have been shown to be resilient against chemotherapy and radiation. They often seed to favorable sites and continue to grow unchecked leading to lethal secondary tumor disease.

XRN2 is upregulated in GBMs as compared to normal and other brain cancer types. XRN2 is a 5'-3' exonuclease that resolve DNA:RNA hybrids (R loops) that arise during transcription, especially at the 3' end of genes. R-loop biology can affect gene expression by modulating the access of genes to transcription factors, miRNA transcription, and methylation status of genes. Our preliminary data have shown that XRN2 is required for cancer cell motility in two GBM cell lines, U87 and U251. It is also required for invasion of G55 cells in vitro.

To understand how XRN2 modulates cell motility and invasion, we conducted RNA-Seq analyses of two GBM cell lines with and without XRN2 expression and found that XRN2 can regulate genes involved in cell motility and invasion pathways. We have conducted a mini-cherry picked screen of the XRN2 targets and found at least 16 genes to be required for cell motility. Some of these XRN2-regulated genes have inhibitors. Our goal is to develop a patient signature that can better predict patient outcome and if possible a new synergetic treatment plan to increase the efficacy of therapies.

TRANSCRIPTIONAL ACTIVATION OF A NOVEL ZEB1-INTEGRIN-ENT1 SIGNALING UNDERLIES THE ROLE OF ZINC TRANSPORTER ZIP4 IN PANCREATIC CANCER CHEMORESISTANCE

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Background: Pancreatic cancer is characterized by local invasion and rapid progression from initiation to metastasis. Most patients will develop chemo-resistance and experience cancer recurrence. Thus, novel strategies derived from a better understanding of molecular events regulating growth and response to therapy are urgently needed.

Methods: In vivo tumor growth and response to gemcitabine treatment were studied with orthotopic xenograft tumor model. Concentrations of gemcitabine in pancreatic cancer cell lines were determined with single cell MS. The interactions between ZIP4 and integrin α3β1 were examined in human pancreatic cancer cells, KPC mouse cell lines, spheroid model and human specimens. The transcriptional regulation of ZEB1, integrins, JNK and ENT1 by ZIP4 was investigated with ChIP and luciferase reporter assays.

Results: ZIP4 predicted survival, promoted cell growth, resistance to chemotherapy, and inhibited the expression of the gemcitabine transporter ENT1 through a ZEB1-dependent upregulation of integrin α3β1 signaling both in human pancreatic cancer cells and a ZEB1 knockout KPC mouse model (KPCZ). Further study showed a requirement for STAT3 in the regulation of ZEB1-integrin axis through direct activation of ZEB1 transcription. Integrins inhibited ENT1 expression through activation of MAPK kinase JNK in pancreatic cancer cells. Finally, in human samples, we demonstrated that ZIP4 expression positively correlated with integrins levels and inversely associated with overall survival of gemcitabine-treated pancreatic cancer cases.

Conclusion: These results provide evidence for a novel pathway induced by ZIP4 controlling pancreatic cancer tumorigenesis and gemcitabine resistance through a ZEB1-integrin-JNK-ENT1 signaling axis. The findings carry high translational value as they may serve as foundation for new personalized therapeutic approaches to treat pancreatic cancer and overcome chemo-resistance.

SEXUAL DIMORPHISMS WITHIN THE TUMOR MICROENVIRONMENT OF COLORECTAL CANCER

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Introduction

Women with colorectal cancer (CRC) have a survival advantage over men, yet mechanisms underlying this are unclear. T cell infiltration within the CRC tumor microenvironment (TME) correlates strongly with survival. We hypothesize that women with CRC have a different immune response with increased T cell infiltration in the TME and differential immune gene expression.

Methods

Tissue microarrays were created using primary tumor, tumor infiltrated lymph nodes, and uninvolved colon from 101 patients. CD4+ and CD8+ cells were identified by immunohistochemistry and digitally counted. Expression of immune-related genes in primary and metastatic CRC was quantified using NanoStringIO360 panel.

Results

Patient age, stage, and location of CRC were not different between the sexes. CD4+ cell counts were higher in samples from women in the tumor (1.7-fold, p=0.004) and lymph nodes (2.0-fold higher, p=0.008). CD8+ frequency was increased in uninvolved colon of women vs. men (47.4% vs. 34.6%, p=0.015), in tumor from women >55 years old vs. younger (40.2% vs 23.4%, p = 0.029), in tumor from stages I/II CRC vs. III/IV (37% vs 23.9%, p =0.009), and was associated with increased survival in all (43.9 months vs 25.3 months, p=0.007). Differential gene expression between men and women was noted in interferon signaling, immune adhesion/migration, and cytotoxicity pathways. Sexual dimorphism in gene expression was more pronounced in metastatic samples.

Conclusions

These data demonstrate significant sexual dimorphism in the immune response to CRC that could contribute to the survival advantage seen in women. Investigation of the mechanisms behind this difference may reveal additional therapeutic targets.

FOCAL ADHERENT KINASE (FAK) IS A VULNERABILITY OF RESIDUAL FIBROTIC STOMA IN THE TRANSGENIC MOUSE MODEL OF KIF5-RET-INDUCED LUNG TUMORS

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Non-small cell lung cancer (NSCLC) usually develops adaptive drug resistance after initially responding to targeted therapy. The evolution of tumors to drug resistance relies on the presence of drug-tolerant tumor cells that survive the initial drug treatment. Thus, reducing the residual tumors is a potential strategy for delaying tumor progression. Doxycycline (Dox)-induced CCSP-rtTA/tetO-KIF5B-RET (C/KR) transgenic mice developed lung adenocarcinoma with desmoplastic reaction. The lung tumors regressed after silencing the KIF5B-RET gene by Dox withdrawal or inhibition of the RET kinase with a RET inhibitor such as nintedanib. However, the responses were incomplete. Notably, the residual tumor cells were often associated the fibrotic stroma. In cell cultures, adhesion to collagen/fibronectin protected the RET fusion+ LC-2/ad cells from the RET protein tyrosine kinase inhibitors, which was alleviated by the FAK inhibitor PND-1186 (VS-4718). To determine the effect of the FAK inhibitor in vivo, we compared Dox-induced C/KR mice subject to Dox withdrawal or Dox withdrawal plus PDN-1186 treatment. Lungs from Dox withdrawal mice had rough surfaces similar to those from nintedanib-treated mice. Remarkably, lungs from Dox withdrawal plus PDN-1186-treated mice had readily visible improvement in the gross appearance with smooth surfaces similar to those of normal healthy lungs. Tissue sections showed that the lungs from PND-1186-treated mice had significantly less residual fibrotic stroma and the associated tumor cells. These results suggest that the desmoplastic stroma provides a niche in the lungs that confers drug tolerance of the tumor cells and illustrated that the FAK inhibitor could reduce the residual fibrotic stroma.

MPS1 EXPRESSION IS CRITICAL FOR CHROMOSOME ORIENTATION AND SEGREGATION IN YEAST WITH HIGH PLOIDY

Ashlea Sartin[1], Madeline Gish[1], Jillian Harsha[1], Dawson Haworth[1], Rebecca LaVictoire[1], and Régis E Meyer[1, *]

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In aneuploid cancer cells, the chromosome segregation apparatus is sensitive to increased chromosome number. The conserved protein kinase, Mps1, is a critical actor of this machinery, orienting the chromosomes properly on the spindle. Abnormally high levels of this kinase have been found in tumors with elevated chromosome number. However, it remains unclear, mechanistically, if and how cells with higher ploidy become dependent upon increased Mps1 levels. To answer these questions, we explored Mps1 dependence in yeast cells with increased sets of chromosomes. We discovered that having more chromosomes affects the ability of cells to orient chromosomes properly. The cells with increased numbers of chromosomes are particularly sensitive to the reduction of Mps1 activity. In mps1 loss of function mutants, cells display an extended prometaphase with a longer spindle and a delay in orienting properly the chromosomes. Altogether, our results suggest that increased numbers of chromosomes render cells more dependent on Mps1 for orienting chromosomes on the spindle. The phenomenon described here may be relevant in understanding why hyperdiploid cancer cells become excessively reliant on high Mps1 expression for successful chromosome segregation.

MODELING ACUTE LYMPHOBLASTIC LEUKEMIA IN ZEBRAFISH WITH TRANSGENIC HUMAN MYC

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Acute lymphoblastic leukemia (ALL) is the most common childhood cancer; B-cell ALL (B-ALL) represents ~85% of cases. Despite its prevalence, until recently robust zebrafish B-ALL models did not exist. The transcription factor MYC, a known oncoprotein, can induce zebrafish T-ALL when expressed as a transgene controlled by a rag2 promoter. However, immature B cells also express rag2, and we discovered fish with transgenic human MYC (hMYC) also develop B-ALL. To distinguish between T- and B-ALL, we use a transgenic fluorescent marker, lck:GFP. In double-transgenic fish, T-ALL fluoresce brightly while B-ALL fluoresce dimly. To compare B- and T-ALL incidence, we monitored over 600 fish by serial fluorescent microscopy and found all fish developed T-ALL (64%), B-ALL (23%), or both (13%) by 10 months. To identify pathways active in both types of ALL, we performed RNA-seq on 10 T- and 14 B-ALL from this model and compared these to T- and B-ALL induced by murine Myc (mMyc). Unexpectedly, we found B-ALL occur in distinct lineages in these lines, with hMYC B-ALL expressing ighz heavy chains, but mMyc B-ALL being ighm-positive. Finally, to investigate glucocorticoid responses, a key component of human ALL therapy, we performed in vivo treatment using dexamethasone (DXM). hMYC B-ALL were highly DXM-sensitive, but many recurred rapidly after treatment ceased. We have also developed techniques to biopsy living fish to obtain normal lymphocytes and ALL cells from various body regions. Overall, our new results expand our understanding of zebrafish hMYC-driven B-ALL, a model of the most important pediatric cancer.

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CANCER
PREVENTION &
CONTROL

1:30 – 2:30 PM   ## SESSION I: Tobacco/E-Cigarette Use and Cessation
Moderator: Amy Cohn, Ph.D.

1:30 – 1:44 PM   **YOUTH USE OF E-CIGARETTES IN THE UNITED STATES: DIFFERENCES IN USER CHARACTERISTICS BY DEVICE TYPE**
Alayna Tackett, PhD
Oklahoma Tobacco Research Center
University of Oklahoma Health Sciences Center

1:45 – 1:59 PM   **ELECTRONIC CIGARETTES AS A HARM REDUCTION STRATEGY: A DNA DAMAGE PERSPECTIVE**
Lurdes Queimado, M.D., Ph.D.
Oklahoma Tobacco Research Center
University of Oklahoma Health Sciences Center

2:00 – 1:14 PM   **ASSESSING COGNITIVE AND EMOTIONAL PROCESSING OF RISK ANTI-HOOKAH MESSAGES AMONG YOUNG ADULTS**
Glenn Leshner, Ph.D.
Gaylord College of Journalism & Mass Communication
University of Oklahoma

2:15 – 2:29 PM   **PANEL/Q&A**

2:30 – 3:30 PM   ## SESSION II: Tobacco/E-Cigarette Use and Cessation
Moderator: Darla Kendzor, Ph.D. & Michael Businelle, Ph.D.

2:30 – -2:44 PM   **A PILOT RANDOMIZED CONTROLLED TRIAL OF A MOBILE JUST-IN-TIME ADAPTIVE INTERVENTION FOR SMOKING CESSATION**
Emily Hébert, Ph.D
Oklahoma Tobacco Research Center
University of Oklahoma Health Sciences Center

2:45 – 2:59 PM   **DARKER SKIN COLOR IS ASSOCIATED WITH A LOWER LIKELIHOOD OF SMOKING CESSATION AMONG MALES BUT NOT FEMALES**
Adam Alexander, Ph.D.
OU Stephenson Cancer Center
University of Oklahoma Health Sciences Center

3:00 – 3:14 PM   **DAILY REPORTS OF SLEEP AND SMOKING ABSTINENCE: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY**
Karen Ra, Ph.D.
OU Stephenson Cancer Center
University of Oklahoma Health Sciences Center

3:15 – 3:29 PM   **PANEL/Q&A**

3:45 – 4:45 PM	**SESSION III: Cancer Screening & Survivorship** **Moderator: Paul Spicer, Ph.D.**
3:45 – 4:14 PM	**COLORECTAL CANCER AND SCREENING ACROSS AMERICAN INDIAN COMMUNITIES** Dorothy Rhoades, MD, MPH OU Stephenson Cancer Center University of Oklahoma Health Sciences Center
4:15 – 4:29 PM	**BREAST CANCER SURVIVORS' POSTURAL SWAY EXCEEDS EXPECTATIONS FOR AGE OR VESTIBULAR PATHOLOGY: A CROSS–SECTIONAL ANALYSIS** Elizabeth Hile, Ph.D. OU Stephenson Cancer Center University of Oklahoma Health Sciences Center
4:30 – 4:44 PM	**PANEL/Q&A**

YOUTH USE OF E-CIGARETTES IN THE UNITED STATES: DIFFERENCES IN USER CHARACTERISTICS BY DEVICE TYPE

Alayna P. Tackett, PhD[1,2], Amanda L. Johnson, MHS[1], Emily T. Hébert, DrPH[1], Elise M. Stevens, PhD[3], Caitlin Smith, MS[1,4], Samantha Wallace, BS[1] and Theodore L. Wagener, PhD[5,6]

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Background: Youth e-cigarette (EC) use has nearly doubled in the last two years. There is a significant lack of research examining youth use of specific EC device types (JUUL, other pod-mod, and tank) and how device type is associated with use.

Methods: A US sample of youth ever EC users (N= 509; 49% male; 70% high schoolers) completed an online survey, including demographic information, history of EC use and dependence (Hooked on Nicotine Checklist [HONC]), perceived harm, and normative perceptions. Associations between device type, demographic, and user characteristics were examined among current (daily, weekly or monthly) users (n = 206; JUUL 58%; other pod-mod 18%; tank 24%) via chi-square tests and bivariate multinomial logistic regression models. Data were weighted to be nationally representative of the US youth population.

Results: JUUL users were more likely to be younger (p<.05) and male (<.05).Tank users were more likely to be Hispanic/Latinx (p <.05). Daily use was most common among JUUL users and JUUL users also had higher average HONC scores (M=4.3) compared to tank users (M=2.6; p<.05) but not other pod-mod users (M=3.9; p=.07). JUUL and tank users were significantly more likely to have initiated use with their current product compared to other pod-mod users (13%; p<.05). Normative perceptions of EC was high, with 53% of youth believing most of their friends would approve of their EC use. Perception of harm varied by EC product used; 50% of JUUL users perceived JUUL as not harmful compared to 33% of other EC users.

Discussion: Daily use and nicotine dependence were more common among JUUL and pod users compared to tank users. These findings are concerning and potentially due to high concentrations of nicotine often found in JUUL and other pod devices. Findings also highlight the normalization of EC use among youth. Further research and longitudinal studies are needed to continue to monitor patterns of EC use among youth.

ELECTRONIC CIGARETTES AS A HARM REDUCTION STRATEGY: A DNA DAMAGE PERSPECTIVE

Lurdes Queimado[1-4], Theodore L. Wagener[3,4], Yan D. Zhao[5], Balaji Sadhasivam[1], Mayilvanan Chinnaiyan[1], Vengatesh Ganapathy[1]

Departments of 1Otolaryngology - Head and Neck Surgery, 2Cell Biology, and 5Biostatistics & Epidemiology; 3The Oklahoma Tobacco Research Center, 4The Peggy and Charles Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma.

Background: Electronic cigarettes (ECs) are the most used tobacco product among youth and are used by over 30% of adult tobacco smokers (dual users). While ECs are often perceived as a safer alternative to tobacco smoking, EC aerosols contain unique constituents that might have unforeseen health consequences. For example, our published in vitro data, now independently validated in an animal model, shows that in addition to causing DNA damage, EC aerosols can reduce DNA repair capacity. Research examining the impact of real world, in vivo, EC use on DNA damage and repair capacity is urgently needed.

Aims: (1) To measure the levels of DNA damage in the oral mucosa of dual users over time; (2) To determine whether the levels of DNA damage vary in function of demographic and clinical variables such as age, sex, EC device characteristics, EC and other tobacco product use behaviors.

Methods: Adult smokers, naïve to EC use, not planning to quit in the next 3 months, were randomized to usual brand cigarette (exclusive tobacco smokers; TS), a second-generation EC device (G2), or a 3rd generation EC device (G3). Follow-up occurred at 1, 4, 12, 26, and 52 weeks after randomization (week zero). Demographics, tobacco history, drug use, and health history was collected at each visit. Oral mucosa cells were collected using a cytobrush. DNA was extracted and damage quantified using q-PADDA as previously reported. The change in DNA damage was analyzed using the paired t-test for each of the three groups, and using the one-way ANOVA model among three groups. Pairwise comparisons were be performed using the Tukey's adjustment in a one-way ANOVA model.

Results: A total of 263 participants have been enrolled, and 168 have been followed regularly for at least 12 weeks. Of these, oral mucosa DNA damage was quantified for at least three time points (week 0, 4 and 12) in 106 participants: 40 exclusive TS, 33 EC G2 users and 33 EC G3 users. Overall, the use of ECs, both G2 and G3, lead to a significant reduction in the number of conventional tobacco cigarettes at 4 and 12 weeks. Dual users of tobacco cigarettes and EC G2 showed a significant reduction in the levels of oral mucosa DNA damage over time. No significant reduction of DNA damage was observed for exclusive tobacco smokers or dual users of tobacco cigarettes and EC G3.

Conclusion: Our data show that the use of ECs by tobacco smokers can lead to a significant reduction in tobacco cigarette use, and may be an effective harm reduction strategy. Our preliminary data suggests that smoking reduction with a G2 leads to a significant reduction in DNA damage, suggesting that the G2 ECs are more effective than G3 in reducing the cancer risk associated with tobacco smoke. Completion of these studies, as well as examination of DNA damage levels after complete switching versus dual use are urgently needed to fully assess the potential of EC G2 and G3 as a harm reduction strategy.

ASSESSING COGNITIVE AND EMOTIONAL PROCESSING OF RISK ANTI-HOOKAH MESSAGES AMONG YOUNG ADULTS

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Affiliations: [1]Gaylord College of Journalism & Mass Communication, University of Oklahoma (location of work); [2] Harvard T.H. Chan School of Public Health, Dana-Farber Cancer Institute, Harvard University, Cambridge, MA; [3]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; [4]School of Business, University of Arkansas-Little Rock; [5]Ohio State University, Columbus, OH.

Hookah tobacco use is a public health concern because it poses substantial health risks, promotes addiction, and is associated with progression to cigarette smoking. Based on exhaustive literature review and pilot testing, we identified message risks/themes to test that target these constructs: 1) health harms, 2) addictiveness, 3) social use, 4) flavoring. Participants' psychophysiological responses were recorded during message exposure in order to get moment-by-moment cognitive and emotional response to different message themes and content. Message development and physiological data collection were funded by an FDA R01 grant 1R01CA229082-01, Darren Mays PI).

Design: A 2 (hookah user status: users/non-users) x 2 (message risk: health risks/addiction risk) x 3 (additional theme: basic (nothing added)/social use/flavoring) x 2 (message repetition) controlled mixed experiment was conducted at the OU PRIME Lab, Center for Applied Social Research, University of Oklahoma. User status is a between-subjects factor, while message risk, additional theme, and message repetition are within-subjects factors.

Dependent variables: 1) Heart rate, measured by electrocardiogram (ECG) as an indicator of cognitive resources allocated to encoding message content; 2) Physiological arousal, measured by skin conductance (GSR) as an indicator of sympathetic nervous system activation; 3) Emotional response, measured by facial action coding system (FACET), a standardized classification system of facial expressions, 4) Visual attention, measured by eye-tracking, with areas of interest set to text areas.

Results: N = 120 participants (61 non-users; 59 users), ages 18-30. Non-users were 65% female (N=40), users were 63% female (N=37). Mean age users = 22.74, SD = 331; mean age non-users= 20.77, SD=2.04. There was a significant quadratic contrast pattern for heart rate (ECG) indicating an orienting response for the theme x time 2-way interaction (p=.001). Plots indicate that the flavor messages show an attenuated orienting response compared to the basic and social messages. However, addiction/social messages showed the worst recognition scores for accuracy (58%, p<.001), suggesting reduced encoding for addiction/social messages. Interestingly, social messages showed both the most positive (p=.007) and negative (p<.001) valence as indexed by FACET. There were no significant differences for any message factors on GSR. Total fixation lengths on primary risk text in the messages, a fundamental eye-tracking metric, were similar across all messages. Across all physiological measures, the best performing messages were an addiction/flavors message, a harms/flavors message, a harms/basic message, and a harms/social message. These messages are candidates for use in an RCT, which is the next phase of the FDA grant.

A PILOT RANDOMIZED CONTROLLED TRIAL OF A MOBILE JUST-IN-TIME ADAPTIVE INTERVENTION FOR SMOKING CESSATION

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Background: Smartphone apps for smoking cessation could offer easily accessible, highly tailored, and intensive interventions at a fraction of the cost of traditional counseling. Although there are hundreds of publicly available smoking cessation apps, few have been empirically evaluated using a randomized controlled trial design. The Smart-T2 app is a just-in-time adaptive intervention that uses EMAs to assess risk for imminent smoking lapse and tailors treatment messages based on risk of lapse and reported symptoms.

Objective: The aims of this 3-armed pilot randomized clinical trial (RCT) were to determine the feasibility and preliminary efficacy of an automated smartphone-based smoking cessation intervention (Smart-T2) relative to standard in-person smoking cessation clinic care and the free NCI QuitGuide smoking cessation app.

Methods: Adult smokers who attended a clinic-based tobacco cessation program were randomized into groups and followed for 13 weeks (1 week pre-quit through 12 weeks post-quit). All study participants received nicotine patches and gum, and all participants were asked to complete EMAs 5 times a day on study provided smartphones for 5 weeks. Participants in the Smart-T2 group received tailored treatment messages at the completion of each EMA. Both Smart-T2 and QuitGuide apps offered on-demand smoking cessation treatment.

Results: Participants (N=81) were 50.6% female, were mostly white (67.9%), were on average 49.6 years old, and smoked on average 22.4 cigarettes per day at baseline. A total of 14 (17.3%) participants were biochemically confirmed 7-day point prevalence abstinent at 12 weeks post-quit (Smart-T2: 22.2%, QuitGuide: 14.8%, Usual Care: 14.8%), with no significant differences across groups. Participants in the Smart-T2 group rated the app positively, with most participants agreeing that they can rely on the app to help them quit smoking and endorsed the belief that the app would help them stay quit, and these responses were not significantly different from the ratings given by participants in the usual care group.

Conclusions: Dynamic smartphone apps that tailor intervention content in real-time may increase user engagement and exposure to treatment related materials. The results of this pilot RCT suggest that smartphone-based smoking cessation treatments may be capable of providing similar outcomes to traditional, in-person counseling.

DARKER SKIN COLOR IS ASSOCIATED WITH A LOWER LIKELIHOOD OF SMOKING CESSATION AMONG MALES BUT NOT FEMALES

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Darker skin color is associated with discrimination and unfair treatment and may contribute to persisting health disparities. This study examined whether darker skin color was associated with smoking cessation and whether this association was moderated by sex and race. This study also explored whether biological and psychosocial factors, including nicotine and cotinine concentrations, discrimination, distrust, and neuroticism, mediated this association. The data for this study came from a prospective smoking cessation intervention that included 224 Black and 225 White adults from Kansas City, Missouri, enrolled between February 2013 and May 2015. Skin color was assessed using a DermaSpectrometer to measure melanin contained within the skin. Point prevalence smoking abstinence was biochemically-verified with salivary cotinine and assessed at weeks 4 and 26. Hierarchical logistic regression analyses were conducted to evaluate hypothesized relations between skin color and smoking cessation. Interactions between race and sex with skin color were also evaluated. While skin color was not associated with smoking cessation in the overall sample or among Blacks only, results indicated that sex moderated the effect of skin color on smoking cessation after adjusting for race and other covariates. Among males, darker skin color was associated with lower odds of achieving smoking abstinence at weeks 4 (OR = 0.60 [95% CI= 0.36, 0.99]) and 26 (OR = 0.52 [95% CI = 0.29, 0.91]). Skin color did not predict smoking cessation among females. Skin color was positively correlated with discrimination (r = 0.15, p = 0.02), cynicism/distrust (r = 0.14, p = 0.03) and neuroticism (r = .24, p < 0.01) among males only. However, these factors did not mediate the association between skin color and smoking cessation. Skin color was not correlated with nicotine or cotinine concentration in the overall sample or among males and females specifically. Skin color may contribute to cessation-related health disparities among Black males, but more research is needed to understand the psychosocial and biological mechanisms through which skin color influences tobacco cessation.

DAILY REPORTS OF SLEEP AND SMOKING ABSTINENCE: AN ECOLOGICAL MOMENTARY ASSESSMENT STUDY

Chaelin K. Ra, Ph.D;[1] Emily T. Hébert, DrPH;[1] Summer Frank-Pearce, Ph.D;[1]Rachel Moisiuc, B.S;[1] Adam C. Alexander, Ph.D;[1] Darla E. Kendzor, Ph.D[1,2] Karen Gamble, Ph.D., [3] Karen Cropsey, Ph.D., [3] & Michael S. Businelle, Ph.D.[1,2]

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Background: There is preliminary evidence that sleep duration and sleep quality are associated with smoking cessation. Yet, few studies have examined mechanisms linking sleep with smoking lapse.

Methods: Data from a pilot three-armed randomized clinical trial of a smartphone-based smoking cessation intervention among adults (N=81) were used to examine mechanisms linking sleep (i.e., hours of sleep each night, sleep quality) and smoking lapse. Participants were loaned a smartphone and asked to complete ecological momentary assessments (EMAs) one week pre-quit and the first 4-weeks following the quit attempt. EMAs assessed daily sleep and wake times, sleep quality, positive and negative affect, smoking urge, stress, and smoking status. Multilevel mediation models were conducted to estimate the associations between sleep, affect, urge, stress, and daily smoking status controlling for age, sex, education, race (White vs. non-White), intervention group, and heaviness of smoking at baseline.

Results: Participants were primarily male (51.2%), White (67.9%), 49.4 years old (SD=12.2), and completed 169 EMAs during the 4-week post-quit period on average. Paths from sleep duration and quality to positive affect, smoking urge, and stress (β=-0.08~0.09, p=.0001~.02) and from positive affect, smoking urge, and stress (β=-0.08~0.18, p=.0001~.09) to daily smoking status were significant. None of the direct effects between sleep quality and duration and daily smoking status were significant. However, the random indirect effects between sleep quality and smoking status via positive affect, smoking urge, and stress (β=-0.02, p=.005; β=-0.02, p=.01; β=-0.01, p=.07 respectively) were significant, suggesting complete mediation.

Conclusion: While sleep duration was related to psychosocial factors that have been previously associated with smoking lapse, there was no direct relationship between sleep duration and daily smoking status. However, results indicated that poor sleep quality may increase risk for smoking lapse through direct effects on positive affect, smoking urge, and stress. Future research should determine if interventions that focus on improving sleep quality during a smoking cessation attempt can increase cessation success rates.

MECHANISTIC INSIGHTS INTO THE ONCOGENIC POTENTIAL OF THE ETV1 Colorectal CANCER AND SCREENING ACROSS AMERICAN INDIAN COMMUNITIES

Authors: Dorothy A. Rhoades, MD, MPH, Department of Medicine and Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Dorothy-Rhoades@ouhsc.edu

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Jessica Blanchard, PhD, Center for Applied Social Research, University of Oklahoma

Tamela Cannady, MHA, Director, Preventative Health, Choctaw Nation of Oklahoma

Jessica Deaton, RN, BSN, RN Care Manager, Oklahoma City Indian Clinic

Effective screening renders colorectal cancer (CRC) a detectable and preventable cause of death, yet CRC remains the second and third leading cause of cancer death respectively among men and women for many American Indian and Alaska Native (AI/AN) communities. The National Cancer Institute noted these disparities in CRC screening and incidence among AI/AN people and funded a CRC screening implementation project for AI communities in Oklahoma, New Mexico, and Arizona, entitled "Dissemination of a Colorectal Cancer Screening Program Across American Indian Communities in the Southern Plains and Southwest United States". This "Cancer Moonshot" project is devoted to understanding challenges and strengths of the processes of care affecting CRC screening, from the client/patient perspective to the clinic and community leadership perspective.

In this multifaceted, collaborative panel presentation, moderated by Dr. Dorothy A. Rhoades, we will provide the following information for the Oklahoma site:

• CRC incidence, mortality, and screening among AI/AN communities, including evidence based guidelines for CRC screening per United States Preventive Services Task Force and The Guide to Community Preventive Services guidelines, including concern for changing guidelines to begin at earlier ages for minority groups (Dr. Rhoades and Dr. Doescher, 10 minutes)

• Processes of care affecting the delivery and uptake of CRC screening, including methods for qualitative data gathering for the CRC screening project (Dr. Blanchard, 10 minutes). (Preliminary data will not be presented).

• Description of proposed dissemination and implementation to include multilevel and multi-component evidence-based strategies for enhancing CRC screening. Examples include individual, social, and systems/organizational level strategies (e.g., small media, provider detailing, navigation) with particular emphasis on clinic-based CRC screening navigation and training. (Dr. Mark Doescher, 10 minutes)

• Tribal/Indian Health care clinic programs, challenges, and successes (community partners from Oklahoma City Indian Clinic and Choctaw Nation Health Services: Ms. Cannady and Ms. Deaton, 10 minutes total)

Learning objectives. At the end of this presentation, participants will be able to:

• Identify geographic disparities in colorectal cancer (CRC) incidence and mortality among American Indians and Alaska Natives in the United States

• Identify evidence based modalities for colorectal cancer (CRC) screening

• Describe multi-level components of processes of care affecting implementation of CRC screening within healthcare settings serving American Indian people

BREAST CANCER SURVIVORS' POSTURAL SWAY EXCEEDS EXPECTATIONS FOR AGE OR VESTIBULAR PATHOLOGY: A CROSS–SECTIONAL ANALYSIS

ES Hile PhD, PT[1]; J Day MA, CPO/LPO[3], C-C Lin PhD, PT[4]; J Dvorak PhD[2]; K Ding PhD[2]; SL. Whitney PhD, PT[5]

OUHSC Colleges of [1]Allied Health & [2]Public Health; [3]OU Medicine Dept of Orthopedic Surgery and Rehabilitation *Oklahoma City, OK;* [4]East Carolina University College of Allied Health Sciences *Greenville, NC;* [5]University of Pittsburgh School of Health and Rehabilitation Sciences *Pittsburgh, PA*

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Background: Published fall rates for breast cancer survivors (BCS), even younger and chemo-naïve women, exceed the 1 in 4 estimated annually for older adults. Balance is known to decline as BCS develop chemo-induced peripheral neuropathy, but many never develop CIPN, so other risk factors must be identified to combat this public health problem. Hypotheses include cancer-related vestibular damage, and multifactorial accelerated aging of postural control.

Purpose: We aim to explore vestibular and accelerated aging theories by quantifying the postural sway response of midlife (35-60 yrs) BCS without CIPN, when standing with vision or distal somatosensation manipulated. We will compare BCS response to that of vestibular patients (VESTIB), and Controls (CON) over age 60 without cancer or neuro-vestibular history.

Methods: This is a secondary analysis of postural sway data from 3 cross-sectional studies of the NIH Toolbox Balance Accelerometry Measure (BAM) Inertial Measurement Unit (IMU). We compared 88 females (mean 61.5 ± 11.9 yrs; range 39-86): 41 Stage 0-III BCS without CIPN, on Aromatase Inhibitors after curative resection, 13 VESTIB, 34 CON. Postural sway was Normalized Path Length (NPL) in Anteroposterior (AP) and Mediolateral (ML) directions while standing for 45 sec Eyes Open (EO) or Closed (EC) with feet: 1) Together 'Narrow,' 2) Heel-to-toe 'Tandem,' 3) Narrow on Foam Cushion 'Narrow Foam'. We normalized sway in each position to Narrow EO. We formed 6 groups by stratifying BCS, VESTIB & CON into Midlife (M) & Older (O) with 60.5 yr cut-off, and compared NPL using Kruskal-Wallis ANOVA on ranks with Bonferroni correction. For post-hoc pairwise comparison we used Wilcoxon rank-sum tests.

Results: In Narrow Foam EC and Tandem EO/EC, normalized AP sway for M-BCS exceeded M-CON (1.5 to 1.9-fold, $p < 0.0001$), M-VESTIB (1.5 to 1.7-fold, $p=0.02$ to 0.004). Further, normalized AP sway in Narrow Foam EC in M-BCS exceeded O-CON (1.6 to 1.7, $p <0.0001$). In the ML direction, M-BCS swayed increased ~1.5-fold more than M-CON, O-CON, M-VESTIB, O-VESTIB (p 0.004 to <0.0001), yet M-BCS sway increased less than all 4 groups in Narrow Foam EO . The most challenging position (Tandem EC) was held by 56% of M-BCS, compared to 75% of M-CON, 29% of M-VESTIB and 20% of O-CON. Narrow Foam EC was held by 60% of O-BCS compared to 87% O-CON.

Conclusions: Midlife BCS without CIPN sway significantly more, especially AP, than both midlife and older controls, but also patients seeking balance rehab for vestibular pathology, yet they perform differently than both older and vestibular cohorts. Findings support further study of postural control in BCS without CIPN, and suggest M-BCS sway most when vision is removed, a finding that informs falls prevention and rehabilitation strategies.

CANCER THERAPEUTICS
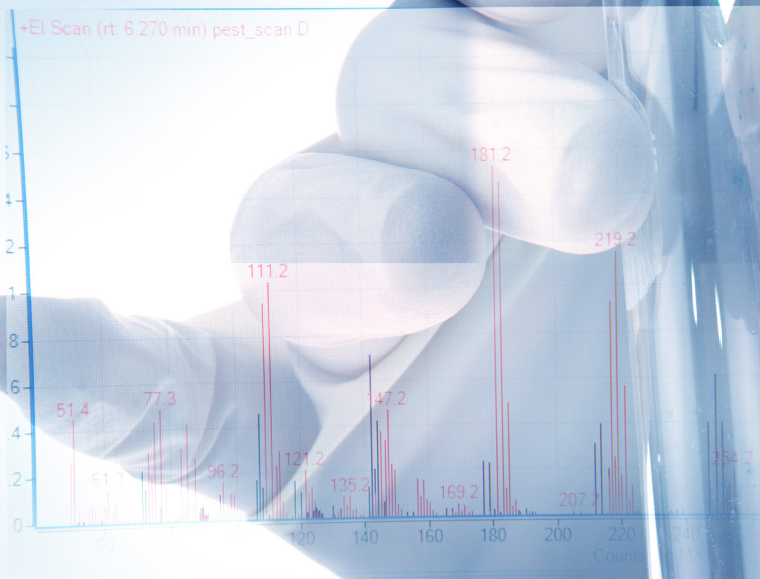
Cancer Therapeutics

1:30 – 2:30 PM   SESSION I
Moderator: Kathleen Moore

1:30 – 1:44 PM   **ACIDIC TUMOR MICROENVIRONMENT TARGETED NANOPARTICLES FOR THE DETECTION OF TRIPLE-NEGATIVE BREAST CANCER BY MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY**
Abhilash Samykutty, PhD
Stephenson School of Biomedical Engineering
University of Oklahoma

1:45 – 1:59 PM   **GAIT SPEED CHANGE IN FIRST CHEMOTHERAPY CYCLE MAY PREDICT LATER DOSE-REDUCTION IN EXPLORATORY ANALYSIS OF OVARIAN CANCER PATIENTS OVER 70**
Anjalika Gandhi, PhD
Department of Gynecologic Oncology
University of Oklahoma Health Sciences Center

2:00 – 1:14 PM   **OUTCOMES OF EARLY STAGE ENDOMETRIAL CANCER IN MEDICALLY COMPLEX WOMEN; HORMONAL CONTROL COMPARED TO TRANSVAGINAL HYSTERECTOMY**
Christina Washington
Department of Gynecologic Oncology
University of Oklahoma Health Sciences Center

2:15 – 2:29 PM   **SINGLE CELL RNA SEQUENCING DELINEATES ACTIVATION OF INNATE AND ADAPTIVE IMMUNE CELLS BY A LOCAL PHOTO-IMMUNOTHERAPY FOR TREATMENT OF METASTATIC MAMMARY TUMORS**
Wei Chen, PhD
Center for Interdisciplinary Biomedical Education and Research
University of Central Oklahoma

2:30 – 3:30 PM   SESSION II
Moderator: Kathleen Moore

2:30 – -2:44 PM   **LASER IMMUNOTHERAPY REQUIRES TYPE I IFNS IN THE TREATMENT OF METASTATIC B16 MELANOMA IN MICE**
Ashley R. Hoover, PhD
Department of Math and Science/ACI
University of Central Oklahoma/Oklahoma Medical Research Foundation

2:45 – 2:59 PM   **IMPACT OF SOCIAL SERVICES ON DEPRESSION AND TREATMENT OUTCOMES AMONGST WOMEN WITH LOCALLY ADVANCED CERVIX CANCER**
Elizabeth Evans, MD
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center

3:00 – 3:14PM   **NOVEL OVARIAN CANCER MAINTENANCE THERAPY TARGETED AT MORTALIN AND MUTANT P53**
Satish Kumar Ramraj, PhD
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center

3:15 – 3:29 PM	**PHASE II TRIAL OF VAGINAL CUFF BRACHYTHERAPY FOLLOWED BY DOSE-DENSE CHEMOTHERAPY IN EARLY STAGE ENDOMETRIAL CANCER PATIENTS WITH ENRICHED, HIGH-INTERMEDIATE RISK FACTORS FOR RECURRENCE** Tara Castellano, MD Department of Gynecologic Oncology OU Stephenson Cancer Center

3:45 – 4:45 PM	**SESSION III** **Moderator: Kathleen Moore**

3:45 – 3:59 PM	**INHIBITION OF GRANULOCYTE COLONY STIMULATING FACTOR EXTENDS SURVIVAL IN AN ADVANCED MODEL OF METASTATIC COLORECTAL CANCER VIA INCREASED ANTI-TUMOR IMMUNE EFFECTS** Anita L. Ray, PhD Department of Surgery University of Oklahoma Health Sciences Center

4:00 – 4:14 PM	**A GLOBAL RNA INTERFERENCE MECHANISM FOR THE TREATMENT OF PROSTATE CANCER** Maria J Ruiz Echevarria, PhD Department of Pathology The University of Oklahoma Health Sciences Center

4:15 – 4:29 PM	**ASSESSMENT OF A SCFV ANTIBODY FRAGMENT AGAINST ELTD1 IN A G55 GLIOBLASTOMA XENOGRAFT MODEL USING A MOLECULAR TARGETING APPROACH** Michelle Zalles Advanced Magnetic Resonance Center Oklahoma Medical Research Foundation

4:30 – 4:44 PM	**ONC201, A TRAIL INDUCING SMALL MOLECULE, PREVENTS INTESTINAL TUMORS IN FAP MOUSE MODEL** Venkateshwar Madka, PhD College of Medicine University of Oklahoma Health Sciences Center

ACIDIC TUMOR MICROENVIRONMENT TARGETED NANOPARTICLES FOR THE DETECTION OF TRIPLE-NEGATIVE BREAST CANCER BY MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY

Presenter: Abhilash Samykutty
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Purpose: Triple-negative breast cancer (TNBC), characterized by tumors without any biomarkers such as estrogen receptor (ER), progesterone receptor (PR), or HER-2 genes. At present, there is no clinically proven, effective therapeutic agent that targets the vulnerability in triple-negative breast cancer. Hence, the development of novel methodologies for early detection as well as better treatment options are essential to improve the prognosis of the disease.

Methods: The Silica nanoparticles with wormhole pore architecture were (WMSN) synthesized by sol-gel chemistry. The WMSN were characterized by transmission electron microscopy (TEM) and dynamic light scattering (DLS). The surface of the WMSN particle was crosslinked with a gatekeeper molecule chitosan (C) and V3 pHLIP peptide to obtain V3-WMSN. The V3-WMSN particle was loaded with propidium Iodide (PI) or IR780 infrared imaging dye. Athymic mice subcutaneously implanted with MDA-MB-468 TNBC cells by the mammary fat pad injection. Once the tumor reaches 3mm in size, athymic mice were intravenously injected with V3-WMSN nanoparticles carrying IR780 dye and were imaged with MSOT.

Results: In the current study, we have synthesized mesoporous silica particles (WMSN) with a diameter of 27 nm. The WMSN was conjugated with chitosan, a pH-sensitive gatekeeper molecule to prevent off-target release. The C conjugated WMSN surface was coupled with pH-sensitive V3 peptide to develop V3-WMSN. The developed V3-WMSN nanoparticle loaded with IR780 or PI dye can detect acidic tumor microenvironment and can penetrate inside the tumor cells. We have developed the in-vivo model of TNBC, MDA-MB-468 cells were injected subcutaneously to the mammary fat pad of the female athymic mice. Once the developed TNBC tumors reach 3mm in size, the V3-WMSN nanoparticles were injected intravenously. The IR780 imaging dye loaded nanoparticles can detect the orthotopically implanted TNBC tumors ($p < 0.0001$, n=5).

Conclusion: Due to the absence of biomarkers, poor prognosis, and limited chemotherapeutic options, TNBC is considered as the most lethal type of breast cancer. The development of silica nanoparticle-based targeted therapies, as well as MSOT based early diagnosis methods, is critical for future therapeutic intervention as well as clinical translation of patients with TNBC.

GAIT SPEED CHANGE IN FIRST CHEMOTHERAPY CYCLE MAY PREDICT LATER DOSE-REDUCTION IN EXPLORATORY ANALYSIS OF OVARIAN CANCER PATIENTS OVER 70

Authors: Elizabeth Hile PhD[1], Anjalika Gandhi MD MS[2], Ana Valente MD[2], Chao Xu PhD[3], Kathleen Moore MD[2]
Institution: University of Oklahoma Health Sciences Center, Stephenson Cancer Center
Departments: [1]Physical Therapy
 [2]Gynecologic Oncology
 [3]Biostatistics and Epidemiology

Objectives: With chemotherapy (chemo) increasingly offered over age 70 in ovarian cancer (OC), clinically feasible predictors of chemo tolerance are needed. We conducted a secondary analysis to explore relationships between grip strength and gait speed trajectories and adverse events (AEs) over the course of chemo in OC patients over age 70.

Methods: We analyzed longitudinal data from 17 women (mean 75.90 ± 4.53 yrs) with Stage III-IV OC in an exercise feasibility study. Grip strength (GRP) & gait speed (GS) were measured before C1, C2, C3 (and after surgery if neoadjuvant). Outcomes of each cycle were 4 dichotomous (Yes/No) adverse events (AE) before next cycle: Hospitalization, Dose Reduction (DR), Treatment Delay, Grade 3-5 Toxicity. After plotting individual GS & GRP trajectories, we calculated GS Change with each cycle (GSChgC1 = V2 GS – V1 GS). We stratified the sample by each AE, and used Wilcoxan rank sum test to compare AE & NO AE groups on GS Chg prior to that cycle. We then transformed GS & GRP Chg to 5-pt scales (±2 = Moderate; ±1 = Small significant; 0 = No change) to test AE associations by Cochran-Armitage Trend Test (CATT). All alpha were 0.05.

Results: Decline in GS with Cycle 1 (GSChgC1) exceeded meaningful change of 0.05 m/s in 58% of women, while GRP declined in 33%. Compared to women with no C3 dose reduction (DR), women with C3 DR (n=3, mean age 73) had 5X greater median GS decline in C1 [GSChgC1 = -0.28 vs -0.05 m/s, p=0.03], but 15X greater median improvement in C2 [+0.36 m/s vs -0.02, p=0.036]. GRP Chg trend was significantly associated with DR after surgery (CATT exact p = <0.001).

Conclusions: In older ovarian cancer patients, large GS decline in chemo cycle 1 may predict need for dose reduction in future cycles, even if GS recovers in cycle 2. These exploratory trajectories warrant further investigation, as they may inform clinical prediction of chemo tolerance.

OUTCOMES OF EARLY STAGE ENDOMETRIAL CANCER IN MEDICALLY COMPLEX WOMEN; HORMONAL CONTROL COMPARED TO TRANSVAGINAL HYSTERECTOMY

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Department of Obstetrics and Gynecology, Division of Gynecologic Oncology
University of Oklahoma Health Sciences Center

In 2018, there will be 63,230 new cases of endometrial cancer diagnosed making it the most common gynecologic malignancy in the United States. The standard approach to early stage endometrial cancer has been a staging hysterectomy. As the gynecologic oncology patient population becomes increasingly obese and comorbid, even a minimally invasive laparoscopic approach is precluded due to challenges. Therefore, we sought to compare transvaginal hysterectomy (TVH) to adjuvant hormonal therapy alone for definitive treatment in medically complex early stage endometrial cancer.

A multi-institutional prospective cohort study of medically complex women with endometrial cancer managed with either hormonal therapy or TVH was performed. Inclusion criteria included women who did not desire fertility and early stage endometrial cancer managed with either a transvaginal hysterectomy or progestin based therapy. Treatment groups were tested for differences in clinical demographics, surgical outcomes, and survival outcomes.

A total of 261 women were screened from 2008-2018. Ninety-nine met inclusion; of those, 81 received a primary TVH and 18 received hormonal treatment alone (HT). Levonorgesterol intrauterine devices (lng-IUD) were used in all HT cases. Median age was 64 (34-85), mean BMI was 46.7average, and mean Charlson comorbidity score was 2.6. Overall, the lng-IUD group was younger (median 63.5 vs 64, p=.49), had a larger mean BMI (45.3 vs 45.8, p=0.30), and had more comorbidities (2.83 vs 2.57, p=0.27). For the TVH cohort, OR time averaged 102 min, estimated blood loss was 300 ml, and the median hospital stay was 2 days. Nine 30-day complications occurred in 4 women; 2 bowel injuries, 3 readmissions, 2 ICU stays and 2 deaths. Deaths were due to bowel injury and post-operative myocardial infarction. In the lng-IUD group, 2 subsequent hysterectomies were performed; one resulted in readmission. Primary lesions resolved in 63% of the lng-IUD cohort in a mean of 8.0 (3.8 – 12.8) months. There were seven recurrences in the TVH group and two in the lng-IUD group with no significant difference between the rates of recurrence.

Medically complex women with early stage endometrial cancer are often poor surgical candidates that will not tolerate robotic/laparoscopic approaches. Our data showed a 5.0% complication risk with transvaginal hysterectomy; therefore, with appropriate counselling transvaginal hysterectomy performed by an experienced surgeon provides a viable option for cancer cure in this cohort of women.

SINGLE CELL RNA SEQUENCING DELINEATES ACTIVATION OF INNATE AND ADAPTIVE IMMUNE CELLS BY A LOCAL PHOTO-IMMUNOTHERAPY FOR TREATMENT OF METASTATIC MAMMARY TUMORS

Wei R. Chen[1], Ashley R. Hoover[1,2], Kaili Liu[1], Christa I. DeVette[3], Jason R. Krawic[3], and William H. Hildebrand[3]

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The ideal strategy for treating metastatic cancers is a systemic, tumor-specific immunity induced by a local intervention. Photo-immunotherapy was developed following this strategy: a local laser irradiation to destroy target tumors and release tumor antigens, followed by an intratumoral administration of an immunostimulant to activate immune cells. Photo-immunotherapy has resulted in eradication of both treated local tumors and untreated distant metastases in our preclinical and preliminary clinical studies. To further understand the immunological mechanism of photo-immunotherapy, we treated highly aggressive, metastatic breast tumors arising in the Mouse Mammary Tumor Virus-Polyoma Middle T (MMTV-PyMT) transgenic model. Photo-immunotherapy resulted in tumor suppression and long-term survival. Furthermore, we observed a large number of infiltrating immune cells and increased immune activities in the treated tumors and secondary lymphoid organs (spleens). To delineate the induced immune responses, we used single cell RNA sequencing (scRNAseq) to analyze the myeloid and lymphoid compartment remodeling in the tumor microenvironment after treatment. Photo-immunotherapy enriched the cytokine signaling pathways, including interferon alpha (IFN), interferon gamma (IFN), and TNF signaling via NFκB, and downregulated Myc targets in innate immune cells. Additionally, photo-immunotherapy enriched similar cytokine signaling pathways in adaptive immune cells, and downregulated mTORC1 signaling, G2M checkpoint, and Myc targets pathways. Since scRNAseq analysis indicated the prominent functions of CD4+ and CD8+ cells downstream of photo-immunotherapy, we tested whether these populations were necessary for tumor inhibition by selectively depleting CD4+ or CD8+ cells before treatment. Our data indicated that CD8+ T cells were required for tumor regression after photo-immunotherapy. Together, our results provided insight to the mechanism of a tumor-specific, long-term immunity induced by a local intervention.

LASER IMMUNOTHERAPY REQUIRES TYPE I IFNS IN THE TREATMENT OF METASTATIC B16 MELANOMA IN MICE

Ashley R. Hoover[1,2], Kaili Liu[1], Xiao-Hong, Sun[2], Wei, R. Chen[1]

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We have developed a novel technique we term laser immunotherapy (LIT). This therapy employs local applications of photothermal therapy (PTT) and an immunological stimulant, N-dihydrogalacochitosan (GC) in order to activate an antitumor immune response. PTT causes tumor necrosis releasing tumor antigens, allowing for the in situ administration of GC to establish a proinflammatory tumor microenvironment. We used LIT to treat B16-F10 tumors in mice. Our experimental results demonstrate that GC activates dendritic cells, macrophages, and other innate cells to activate the adaptive immune response. Specifically, we found that bone marrow derived dendritic cells (BMDCs) stimulated with GC produced type I IFNs and IL-1β. Furthermore, Type I IFNs were proven critical for LIT generated antitumor immunity as IFNaR1 deficient animals bearing B16-F10 melanoma tumors failed to respond to LIT treatment. In our in vitro experiments, GC induced type I IFNs through STING as STING-deficient BMDCs failed to produce type IFNs. In vivo, STING-deficient mice bearing B16-F10 tumors had similar survival rates as that of the heterozygous controls following LIT treatment. However, tumor re-challenging experiments revealed that LIT-cured STING-deficient animals had significantly higher tumor growth rate than LIT-cured heterozygous animals, indicating immune memory is likely impaired without STING. Our results are consistent with studies demonstrating the importance of type I IFN produced by DCs for cross-priming of CD8 T cells, antitumor immunity, and memory formation. These findings could help understand the immunological mechanism of laser immunotherapy and move this novel therapy closer to clinical applications.

IMPACT OF SOCIAL SERVICES ON DEPRESSION AND TREATMENT OUTCOMES AMONGST WOMEN WITH LOCALLY ADVANCED CERVIX CANCER

ET Evans[a], KG Essel[a], SE Johnston[a], D Zhao[a], KN Moore[b], LL Holman[b]

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Objectives: To examine the impact of interventions targeted at depression and socio-demographic barriers to care on outcomes of patients with locally advanced cervical cancer (LACC) undergoing primary chemoradiation.

Methods: We conducted a retrospective review of all patients (pts) undergoing primary chemoradiation for LACC at a single tertiary care center from January 2017 to January 2019. The Patient Health Questionnaire-9 (PHQ-9) is a screening tool for depression that has been validated for use in cancer pts. It includes a broad spectrum of major depressive disorder symptoms and consists of a scale from 0-27. PHQ-9 scores obtained at the initial visit and following treatment completion were reviewed. Social services (SS) available included medication assistance, financial assistance, transportation assistance, emergency funds, lodging, and insurance registration.

Results: Of the 55 pts who met inclusion criteria, median age of diagnosis was 47 years (range, 27-82); 36 pts (65%) were Caucasian and 22 pts (40%) were stage IB. At the time of initial visit, median PHQ-9 score was 7.5 (range, 0-25) and 14 pts (25.45%) had a score of 15 or more. Following treatment completion, the PHQ-9 score had improved by 2.17 points with a median PHQ-9 score 5 (range, 0-27). Thirty-seven pts (67.27%) utilized at least one SS. Higher initial PHQ-9 score resulted in an increased risk of death; for every point in initial PHQ-9 score, the risk of death increased by 15% (p=0.03). Higher PHQ-9 score at diagnosis was associated with higher pain scores (p=0.02). A drop in PHQ-9 from initial evaluation to post-treatment evaluation was associated with an improvement in pain scores (p=0.03). Pts who utilized SS trended toward a PHQ-9 decrease of 2.50 points, while those who did not trended toward a PHQ-9 increase of 1.50 points (p=0.66). When stratified by median income for zipcode, pts with a median income < $50,000 who utilized SS experienced a PHQ-9 score drop of 4 points, whereas those who did not resulted in a PHQ-9 score increase of 1.5 points, though this was not significant (p=0.09). Time to completion of therapy, distance from hospital, and insurance status were not associated with initial PHQ-9 score or a change in PHQ-9 score (p>0.05).

Conclusion: Increased PHQ-9 scores, as a measurement of depression, are associated with worse outcomes amongst pts with LACC undergoing primary chemoradiation. Efforts targeted at alleviating social and demographic barriers to care may improve PHQ-9 scores amongst the most resource poor patients.

NOVEL OVARIAN CANCER MAINTENANCE THERAPY TARGETED AT MORTALIN AND MUTANT P53

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Current ovarian cancer maintenance therapy is limited by toxicity and no proven impact on overall survival. To study a maintenance strategy targeted at missense mutant p53, we hypothesized that release of mutant p53 from mortalin inhibition by the SHetA2 drug combined with reactivation of mutant p53 with the PRIMA-1MET drug inhibits growth and tumor establishment synergistically in a mutant-p53 dependent manner. The Cancer Genome Atlas (TCGA) data and serous ovarian tumors were evaluated for TP53 and HSPA9/mortalin status. SHetA2 and PRIMA-1MET were tested in ovarian cancer cell lines and fallopian tube secretory epithelial cells using isobolograms, fluorescent cytometry, western blots and ELISAs. Drugs were administered to mice after intraperitoneal injection of MESOV mutant p53 ovarian cancer cells and prior to tumor establishment, which was evaluated by logistic regression. Fifty-eight percent of TP53 mutations were missense and there were no mortalin mutations in TCGA high-grade serous ovarian cancers. Mortalin levels were sequentially increased in serous benign, borderline and carcinoma tumors. SHetA2 caused p53 nuclear and mitochondrial accumulation in cancer, but not in healthy, cells. Endogenous or exogenous mutant p53 increased SHetA2 resistance. PRIMA-1MET decreased this resistance and interacted synergistically with SHetA2 in mutant and wild type p53-expressing cell lines in association with elevated ROS/ATP ratios. Tumor-free rates in animals were 0% (controls), 25% (PRIMA1MET), 42% (SHetA2) and 67% (combination). SHetA2 (p=0.004) and PRIMA1MET
(p=0.048) functioned additively in preventing tumor development with no observed toxicity. These results justify development of SHetA2 and PRIMA-1MET alone and in combination for ovarian cancer maintenance therapy.

PHASE II TRIAL OF VAGINAL CUFF BRACHYTHERAPY FOLLOWED BY DOSE-DENSE CHEMOTHERAPY IN EARLY STAGE ENDOMETRIAL CANCER PATIENTS WITH ENRICHED, HIGH-INTERMEDIATE RISK FACTORS FOR RECURRENCE

Tara Castellano, John Maxwell, IV, Adam Walter, J. Spencer Thompson, D. Scott McMeekin, and Lisa M. Landrum.

Objective: To determine the feasibility of treatment with vaginal cuff brachytherapy (VCB) followed by 3 cycles of dose dense paclitaxel and carboplatin chemotherapy (ddPC) in an enriched, high-intermediate risk population of patients with early stage endometrial cancer following at least hysterectomy.

Methods: A phase II clinical trial of patients with presumed early stage endometrial cancer were treated with VCB (2100 cGy) followed by three cycles of carboplatin (AUC 6) and paclitaxel (175 mg/m2) following surgery. The primary endpoint was proportion of patient completing both VCB and ddPC. Based on the 87% and 91% completion of therapy rates in the GOG 249 protocol arms, the regimen will be considered feasible if 85% of enrolled patients complete the study. Secondary outcomes include short and long term treatment toxicities, recurrence rate, and progression free survival. Toxicity assessments were patient reported as well as those resulting in delays or dose modifications.

Results: 39 patients were screened, of the 32 evaluable patients included, the median age was 64.5, the median BMI was 35.1, a majority 18/32 (56.3%) were pure endometrioid histology, 18/32 (52.4%) were stage Ib, and 21/32 (65.6%) were fully staged including lymphadenectomy. In total, 4/32 (12.5%) participants were removed from study for renal insufficiency, paclitaxel reaction, treatment refusal and withdrawal of consent. Median time to VCB completion was 11 days with 29/32 (90.6%) patients completing all three fractions of VCB. Acute toxicities with VCB included fatigue (19%) and dysuria (19%). In total, 28/32 (87.5%) received any chemotherapy and 26/32 (81.3%) completed three cycles without delay. Grade 3 or 4 ddCT toxicities included decreased ANC (17%) and infusion reaction (10%). At a median follow-up of 11 months, 91% of patients remained progression free. Three patients experienced a recurrence; they occurred both locally and distant.

Conclusions: Adjuvant therapy with both VCB and chemotherapy is feasible and well-tolerated in a high risk population with endometrial carcinoma. Data collection and maturation is ongoing.

INHIBITION OF GRANULOCYTE COLONY STIMULATING FACTOR EXTENDS SURVIVAL IN AN ADVANCED MODEL OF METASTATIC COLORECTAL CANCER VIA INCREASED ANTI-TUMOR IMMUNE EFFECTS

Anita L. Ray, Robert A. Nofchissey, Megan Reidy, Apryl Saunders, Maaz Khan, Shaoxuan Guo, Megan Lerner, Katherine T. Morris,
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Background: Recombinant granulocyte colony stimulating factor (GCSF) has been used to treat and prevent chemotherapy-associated febrile neutropenia since 1991. However, many solid tumors, including colorectal cancer (CRC), have increased expression of the GCSF receptor. Furthermore, GCSF treatment enhances tumor proliferation, migration, and the stem-like cell compartment *in vitro*. GCSF inhibition with functional antibody decreased CRC neoplasm development in a relevant immune competent mouse model and was associated with significant changes in the tumor immune microenvironment (TIME). The aim of this study was to assess the effects of anti-GCSF antibody on survival and the TIME in an advanced model of peritoneal CRC carcinomatosis.

Methods: Six-week old male and female C57Bl/6J (B6) mice underwent intraperitoneal (IP) injection with 1×10^5 MC38 cells (a validated syngeneic colon cancer cell line). After 7 days, 3x/week IP treatments of anti-GCSF antibody vs isotype control were administered until sacrifice which was performed when mice met a priori criteria as moribund. Tumors and blood were harvested at sacrifice and flow cytometry, multi-plex bead-based array and immunohistochemistry were performed.

Results: Survival was increased by 50% with one mouse surviving with minimal tumor burden until scheduled euthanasia in the anti-GCSF antibody treatment group. Antibody treated mice had significant increases in total CD8+ cell infiltration with increased IFNγ responses. In addition, antibody treatment significantly decreased tumor Treg infiltration and increased the number of PD1+ T cells in the TIME.

Conclusions: Single agent anti-GCSF antibody treatment increased survival in an advanced model of peritoneal CRC carcinomatosis. Furthermore, the resulting changes in the TIME suggest a significant potential for synergy between this approach and PD1 inhibition.

A GLOBAL RNA INTERFERENCE MECHANISM FOR THE TREATMENT OF PROSTATE CANCER

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The treatment of advanced prostate cancer (PCa) remains a major clinical challenge. Androgen deprivation therapy (ADT) which blocks ligand activation of the androgen receptor (AR) is the standard treatment, but, while it is initially effective, most patients relapse with lethal castration resistant PCa (CRPC). New therapeutic approaches are therefore critical to successfully manage the disease. Development of resistance to ADT requires reactivation of AR-signaling, and involves various mechanisms, including AR amplification and changes in the expression/activity of AR-coregulators. Studies from our lab have identified a cell killing mechanism in PCa cells that relies on large-scale RNA interference (RNAi) of a network of AR coregulators. We will present in vitro and in vivo data that led to the characterization of this mechanism and discuss future implications for the development of a therapeutic approach for CRPC.

ASSESSMENT OF A SCFV ANTIBODY FRAGMENT AGAINST ELTD1 IN A G55 GLIOBLASTOMA XENOGRAFT MODEL USING A MOLECULAR TARGETING APPROACH

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Introduction: Glioblastoma multiform (GBM) is a very aggressive form of cancer and an estimated 16,000 patients die of glioblastomas in the US annually.[1] Although high-grade glioblastomas are the most common ***primary*** brain tumors found in adults, the therapeutic approaches available do not significantly increase the prognosis for the patients, with the average survival limited to around 14 months.[2] ELTD1 (epidermal growth factor, latrophilin, and 7 transmembrane domain containing protein 1 on chromosome 1) is a biomarker for angiogenesis, found to be highly expressed in human high-grade gliomas.   We have also previously shown that a polyclonal antibody therapy against ELTD1 is effective in significantly increasing animal survival, decreasing tumor volumes, and decreasing angiogenesis in a nude mouse G55 xenograft GBM (glioblastoma) model. This study focuses on the optimization of targeting ELTD1 through the use of molecular-targeted MRI (mtMRI) in vivo in a xenograft G55 GBM model.

Methods: Athymic Nude Fox1nu mice were intracerebrally injected with human G55 cells. Morphological magnetic resonance imaging (MRI done on a Bruker Biospec 7.0 Tesla/30 cm horizontal-bore imaging system) was used to monitor and calculate tumor volumes every 3-4 days. Once tumors were detected, 6-7 mm3 in size, they were treated with 2mg/kg of monoclonal anti-ELDT1 antibody or scFv anti-ELDT1 antibody via tail-injection. All treatments continued until the tumor volume reached 150 mm3. Perfusion images obtained at tumor detection and before termination were used to assess microvasculature alterations. Molecular targeting against ELTD1 was performed with a molecular probe previously described by our group. Untreated mice were injected via tail-vein with either a non-specific mouse IgG isotype contrast agent (IgG-albumin-Gd-DTPA-biotin; IgG contrast agent), monoclonal anti-ELTD1 probe or fragment anti-ELTD1 attached probe. Glioma-bearing mice were anesthetized with isoflurane (2-3%) for treatments or anti-ELTD1 probe administration, and for MRI scans. All mice were terminated upon their last MRI imaging session and their tissue was taken for histology. IHC for anti-CD34 anti- body (rabbit anti-CD34, 10 µg/mL; #ab81289, Abcam) was performed to assess microvessel density measurements using the Aperio ScanScope Image Analysis System.

Results: The percent survival post tumor detection of G55-glioma bearing mice was significantly higher with both the mAb (p=0.0058) and fragment (p=0.0001) treatment compared to the untreated control (average survival ~9 days). Tumor volumes at day 9 post tumor detection were significantly lower with the anti-ELTD1 treated mice (mAb p=0.0009; fragment p=0.017) when compared with untreated controls. We then examined whether the treatments had an effect on the microvasculature. MRI perfusion scans demonstrated a characteristic decrease in rCBF in the tumor region of untreated animals depicting increased angiogenesis. The perfusion values in mice treated with anti-ELTD1 treatments were significantly improved when compared to untreated (p<0.0001 for both). We then sought to characterize the effect of our anti-ELTD1 treatment on the tumor associated vasculature. Both of the anti-ELTD1 therapy significantly decreased the microvessel density levels (MVD) (p<0.0001) in the tumor region when compared to control.

Next, we examined whether our antibody treatment had an effect on Notch. Tissue from glioma-bearing mice from each group was stained with Notch1 and the positivity was analyzed. The Notch1 positivity levels in the contralateral tissue were significantly lower (p<0.0001) when compared to the levels in the tumor region. Furthermore, our monoclonal and fragment anti-ELTD1 treatments were successful in significantly decreasing Notch1 levels (p=0.0001 and p<0.0001 respectively) within the tumor region and bringing them down to contralateral levels.

We then moved onto molecular targeting to determine whether our antibody treatments were crossing the BBB and were responsible for the previous results shown above. We attached either non-specific IgG, monoclonal anti-ELTD1, or the scFv fragment onto our molecular probe previously described (albumin-biotin-Gd-DTPA). The molecular probes were injected via tail-vein into untreated glioma-bearing animals and were monitored via MR molecular targeting imaging. Differences in signal intensity were significantly higher for the monoclonal and fragment attached molecular probes (p=0.0007 and p=0.0038 respectively) compared to IgG control.

Our fragment-attached probe was found to bind onto some regions not initially classified as tumor tissue. The tissue was then stained with SA-HRP, which binds onto the biotin tag attached on the molecular probe, to further examine said regions. Our fragment-attached probe was successful in reaching the bulk tumor as shown through SA-HRP. Furthermore, H&E analysis of the tissue discovered that there were extremely diffuse tumor regions along the lateral cortex regions of the brain, which our probe successfully bound onto. We were also able to find our molecular probe through SA-HRP staining in the diffuse tumor regions.

Discussion: Targeting ELTD1, a biomarker for angiogenesis, with varying antibodies resulted in increased survival and decreased tumor volumes in a G55 xenograft GBM mouse model. Our antibody treatments were also successful in decreasing and normalizing the vasculature. Additionally, our antibody treatments were effective in decreasing Notch1 levels and bringing them back to contralateral levels. Through the use of mtMRI, we were able to determine altered levels of binding specificity against the tumor region using different anti-ELTD1 attached probes (monoclonal and scFv fragment antibodies). Our scFv attached probe, however as not only able to reach and bind onto the bulk tumor areas, but it was also successful in reaching diffuse tumor areas. Our data suggest that the optimization of an anti-ELTD1 therapy could be used to have better treat against angiogenesis in glioblastomas. Additionally, our molecular targeting data demonstrates the future diagnostic potential of our scFv antibody fragment against ELTD1 for distinguishing diffuse tumors that are undetectable through MR imaging.

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ONC201, A TRAIL INDUCING SMALL MOLECULE, PREVENTS INTESTINAL TUMORS IN FAP MOUSE MODEL

Venkateshwar Madka[1], Yuting Zhang[1], Gopal Pathuri[1], Janani Pannerselavam[1], Nicole Stratton[1], Adam S Asch[2], Chinthalapally V. Rao[1]

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Colorectal cancer (CRC) is a major health problem globally. Preventing CRC in the general population, and especially in high-risk cohorts with colonic polyps, or its recurrence, is a high priority. ONC201, an orally active small molecule with robust antitumor activity, is currently in clinical trials for advanced cancers. The aim of this study was to determine the CRC preventive potential of ONC201 using the $Apc^{min/+}$ mouse model for CRC in familial adenomatous polyposis. First, the optimal and non-toxic doses of ONC201 were determined. C57BL/6J mice (n=6/group) were randomized, and five different doses of ONC201 (0-100mg/kg BW) were administered orally twice a week by gavage. After six weeks of treatment, all mice were euthanized, and tissues were analyzed for optimal dose and toxicity. Based on the body weight gain, gross organ weights at termination, blood profiling, plasma liver enzyme profile, and histopathological analysis, it was concluded that there were no toxicities associated with ONC201 within the tested dose range. For efficacy evaluation, $Apc^{min/+}$ male and female mice (n≥20) were grouped and ONC201 (0, 25 and 50 mg/kg BW) was administered by gavage, twice weekly for 14 weeks. At termination, intestinal tumors were evaluated for incidence and multiplicity to determine the efficacy of ONC201. Results indicate a strong suppressive effect of ONC201 against colonic and small intestinal (SI) tumor multiplicity in mice of both genders. Colonic tumor incidence was significantly reduced by >50% in ONC201-treated (50 mg/kg BW) male ($p<0.0002$) and female mice ($p<0.001$) when compared with placebo. Colonic tumor multiplicity was reduced by 68% in ONC201-treated (50 mg/kg BW) male mice ($p<0.0001$) and by 75% in female mice ($p<0.0003$). SI polyps were suppressed by up to 68% in both male mice ($p<0.0001$) and female mice ($p<0.0001$). Snap-frozen colon tumor samples were analyzed for various biomarkers. Western blot protein analysis of the tumors suggested a dose-dependent increase in TRAIL expression upon treatment with ONC201. Similar increases were observed for DR5 and cleaved caspase 8 protein expression. Cleaved caspase 7, caspase 3, FADD and p21 were found to be increased in the treated tumor samples when compared with control. Immunohistochemical analysis indicated a significant decrease in PCNA index in the ONC201-treated tumors compared with controls. Serum analysis indicated a decrease in pro-inflammatory biomarkers, such as IL1β, IL6, TNFα, G-CSF, and GM-CSF, in the ONC201-treated samples compared to controls. Overall, chronic oral administration of ONC201 demonstrated strong chemopreventive efficacy against intestinal tumorigenesis in the $Apc^{min/+}$ mouse model. (*Supported by NCI* PREVENT program)
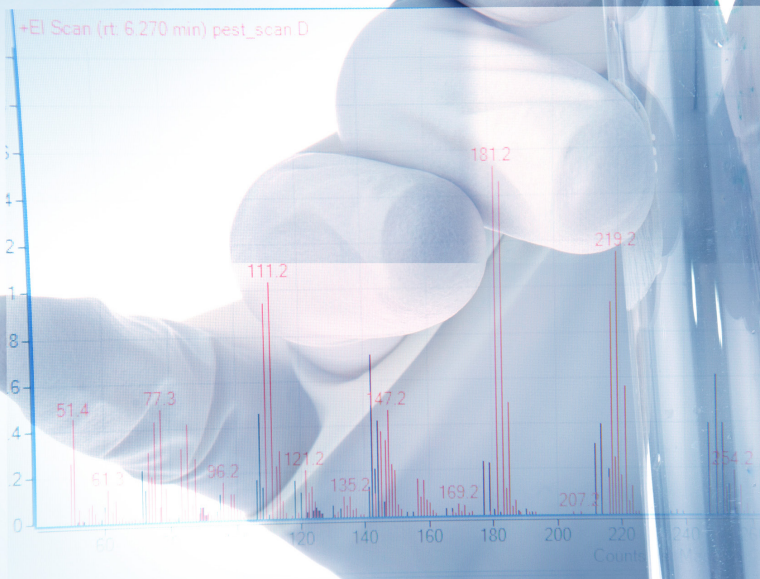
POSTER
PRESENTATION

Cancer Research Symposium Poster Session
10:30 am – 12:00 pm
Level 1

Poster Presentation List (listed A to Z by presenter last name)	Track & Board Number
BRG1 (SMARC4) INFLUENCES THE RESPONSE TO EGFR INHIBITORS IN LUNG CANCER Ahmed, Rebaz	CB 1
A NOVEL T-ALL TUMOR SUPRESSOR - OSR2 Andrade, Pilar	CB 2
CONFINED SPACE MIGRATION CAN FACILITATE THERAPY RESISTANCE AND GENE EXPRESSION CHANGES IN GLIOBLASTOMA MULTIFORME Babu, Anish	CT 42
CIGARETTE SMOKE INDUCES GOBLET CELL METAPLASIA IN HUMAN AIRWAY EPITHELIAL CELLS IN A NOTCH-DEPENDENT MANNER Bodas, Manish	CB 3
SHETA2 INCREASES THE ACTIVITY OF PALBOCICLIB IN CERVICAL CANCER IN VITRO AND IN VIVO Bosley, Amy	CT 43
TOBACCO USE IN LAO PEOPLE'S DEMOCRATIC REPUBLIC Bui, Thanh	CPC 21
MECHANISMS OF RESISTANCE TO THE ALLOSTERIC SHP2 INHIBITOR RMC-4550 Chen, Jianhua	CB 4
QUANTIFICATION OF DNA DAMAGE ON HPRT AS A BIOMARKER OF CANCER RISK Chinnaiyan, Mayilvanan	CPC 22
RNAI SEED-BASED APPROACH TO TARGET ANDROGEN SIGNALING NETWORKS TO INDUCE CELL DEATH IN PROSTATE CANCER CELLS Corbin, Joshua	CB 5

THE IMPACT OF SURGICAL DELAY ON BREAST CANCER RECURRENCE: A SEER-MEDICARE ANALYSIS Crowell, Marielle	CPC 23
INVESTIGATING THE GENOMIC STABILITY OF INDUCED PLURIPOTENT STEM CELLS IN LONG TERM CULTURE DuBose, Casey	CB 6
PROGNOSTIC FACTORS FOR RESPONSE TO CHEMOTHERAPY IN PATIENTS WITH ADVANCED OR RECURRENT ENDOMETRIAL CANCER Essel, Kathleen	CT 44
CLEAR CELL CARCINOMA OF THE OVARY TREATED WITH PEPTIDE-TARGETED MESOPOROUS SILICA NANOPARTICLES Frickenstein, Alex	CT 45
ECIG AEROSOL ALTERS ANTI-OXIDANT AND DETOXIFYING ENZYME EXPRESSION LEVELS IN THE HUMAN ORAL EPITHELIAL CELLS Ganapathy, Vengatesh	CPC 24
PREVALENCE AND ASSOCIATIONS OF PELVIC FLOOR DYSFUNCTION IN CERVICAL CANCER SURVIVORS Greenwood, Ashly	CT 46
ROLE OF MRTFS IN CANCER ASSOCIATED FIBROBLASTS IN METASTATIC COLORECTAL CANCER Griffith, James	CT 47
INVESTIGATION OF ANTI-CANCER DRUG RESISTANCE IN OVARIAN CANCER SPHEROIDS Gunay, Gokhan	CB 7
THE EFFECT OF EXTRACELLULAR SELF-ASSEMBLY OF MMP-9 RESPONSIVE SUPRAMOLECULAR STRUCTURES ON OVARIAN CANCER CELLS Hamsici, Seren	CB 8
ABNORMAL LYMPHOPOESIS PRECEDES THE ONSET OF ALL IN HMYC TRANSGENIC ZEBRAFISH Hasan, Ameera	CB 9
A MACHINE LEARNING APPROACH TO IDENTIFYING RESPONSE FATIGUE AND NON-COMPLIANCE IN ECOLOGICAL MOMENTARY ASSESSMENT Hébert, Emily (Mathews, Ashely)	CPC 25

MOHS MICROGRAPHIC SURGERY FOR SQUAMOID ECCRINE DUCTAL CARCINOMA: A CASE REPORT
Hornback, Cheyenne

CT
48

COMMON AND DISTINCT TRANSCRIPTOMIC FEATURES OF LUNG TUMORS INDUCED BY THE
EGFR(L858R) AND KIF5B-RET PROTEIN TYROSINE KINASE ONCOGENES IN TRANSGENIC MICE
Hu, Xueqing

CB
10

COPPER-64 PET IMAGING OF THE CXCR4 CHEMOKINE RECEPTOR USING A CROSS-BRIDGED
CYCLAM BIS-TETRAAZAMACROCYCLIC CHEMOKINE RECEPTOR ANTAGONIST
Hubin, Tim

CT
49

CHEROKEE NATION HEALTH ANALYTICS CORE: LINKING CANCER REGISTRY AND ELECTRONIC
MEDICAL RECORD DATA
Janitz, Amanda

CPC
26

END-OF-LIFE SERVICES IN TRIBAL COMMUNITIES
Jervis, Lori

CPC
27

ER/PR + BREAST CANCER TREATMENT BY PH RESPONSIVE MESOPOROUS SILICA NANOPARTICLES
Jones, Meredith

CT
50

NAPROXEN BLOCKS SPONTANEOUS LUNG ADENOMA PROGRESSION TO ADENOCARCINOMA IN
KRAS-G12V MICE
Kumar, Gaurav

CPC
28

PHARMACOLOGICAL MODULATION OF INFLAMMATION AND P53 SIGNALING SYNERGIZE TO
PREVENTS MUSCLE INVASIVE BLADDER CANCER IN-VIVO
Kumar, Nandini

CT
51

HIGH-DIMENSIONAL ANALYSIS OF TUMOR-INFILTRATING IMMUNE CELLS IN TREATMENT OF
BREAST CANCER USING LASER IMMUNOTHERAPY
Liu, Kaili

CT
52

TUMOR-TARGETED, PH-RESPONSIVE SILICA NANOPARTICLE AS A VEHICLE FOR IDENTIFICATION OF
PANCREATIC CANCER VIA OPTOACOUSTIC IMAGING
MacCuaig, William

CT
53

Poster Presentation List (cont.)
(listed A to Z by presenter last name)

EFFECTS OF E-CIGARETTE AEROSOL EXTRACTS ON CYTOCHROME P450 MONO-OXYGENASE ENZYMES Manyanga, Jimmy	CB 11
HISTO-MORPHOLOGIC CHARACTERISTICS OF THE POST BIOPSY SITE OF BREAST TUMORS McCarty, Cruz	CB 12
RACIAL SEGREGATION AND DISPARITIES IN TIMELY SURGERY IN BREAST CANCER PATIENTS Mesiya, Sidra	CPC 29
THE ROLE OF NECROPTOSIS IN HEPATOCELLULAR CARCINOMA Mohammed Jazir, Sabira	CB 13
THE BIOLOGICAL IMPACT OF THE GOLGI MEMBRANE PROTEIN TMEM165 FOR BREAST CANCER Murali, Pavitra	CB 14
CASE REPORT OF INTRAMUSCULAR DRY NEEDLING-ELECTRICAL STIMULATION FOR IMPAIRED HAND FUNCTION AFTER BRAIN TUMOR RESECTION Neuhold, Rachel	CPC 30
ALCOHOL EXCISE TAXES AS A PERCENTAGE OF PRICES IN OECD COUNTRIES Ngo, Anh	CPC 31
FACTORS ASSOCIATED WITH PALLIATIVE CARE KNOWLEDGE AMONG AMERICAN ADULTS Ogunsanya, Motolani	CPC 32
SUBJECTIVE SOCIAL STATUS INDIRECTLY INFLUENCES SHORT-TERM SMOKING CESSATION THROUGH NICOTINE WITHDRAWAL SYMPTOMS Olurotimi, Oluwakemi	CPC 33
USING GROWTH CURVE MODELLING TO ELUCIDATE THE ROLE OF AFFECT IN SMOKING CESSATION Ra, Karen	CPC 34
DISCOVERY AND DEVELOPMENT OF DUAL MPGES-1 AND 5-LOX INHIBITOR LFA-9 AS A COLON CANCER CHEMOPREVENTIVE AND ANTI-INFLAMMATORY AGENT S. Yarla, Nagendra	CT 54

DNA DAMAGE DETECTION BY Q-PADDA: A PROMISING TOOL FOR ASSESSMENT OF CERVICAL CANCER RISK
Sadhasivam, Balaji

CPC
35

A COMPARISON OF DELAY DISCOUNTING BY E-CIGARETTE AND CIGARETTE USERS: IMPLICATIONS FOR U.S. FOOD AND DRUG ADMINISTRATION'S REGULATORY IMPACT ANALYSIS
Shang, Ce

CPC
36

STELLATE CELLS DERIVED HGF UNDER HYPOXIA RE-ACTIVATES P13K/AKT PATHWAY AND CONTRIBUTES TO THE LIMITED SENSITIVITY OF EDFR INHIBITOR IN PANCREATIC CANCER
Shi, Xiuhui

CB
15

THE EFFECTS OF ELECTRONIC CIGARETTE FLAVORS ON WEIGHT GAIN AMONG CIGARETTE SMOKERS IN A SWITCHING TRIAL
Smith, Caitlin

CPC
37

GENETICALLY ENGINEERED TRAIL DELIVERY TARGETING DEATH-RECEPTORS FOR THERAPY RESISTANT PROGRESSIVE NEUROBLASTOMA
Somasundaram, Dinesh Babu

CB
16

OPPOSITE ROLES OF THE JMJD1A INTERACTION PARTNERS MDFI AND MDFIC IN COLORECTAL CANCER
Sui, Yuan

CB
17

MOBILITY-RELATED BASIC AND INSTRUMENTAL ACTIVITIES OF DAILY LIVING FLUCTUATE OVER 2-3 CYCLES OF CHEMOTHERAPY FOR OVARIAN CANCER IN WOMEN OVER 70: AN EXPLORATORY ANALYSIS
Valente, Ana

CPC
38

SUSCEPTIBILITY TO E-CIGARETTE USE AMONG YOUTH IN THE UNITED STATES: AN UPDATE FROM THE 2018 NATIONAL YOUTH TOBACCO SURVEY
Wallace, Samantha

CPC
39

FEASIBILITY STUDY OF OPTICAL COHERENCE TOMOGRAPHY FOR PERCUTANEOUS NEPHROLITHOTOMY GUIDANCE
Wang, Chen

CT
55

MECHANISMS LINKING PAIN AND SMOKING DURING A QUIT ATTEMPT Waring, Joseph	CPC 40
TREATMENT OF BREAST CANCER TUMORS AND LEUKEMIA WITH NOVEL ANNEXIN A5 - DRUG CONJUGATES Woodward, Alexis	CT 56
CANCER STEM CELL MARKER DCLK1 CORRELATES WITH TUMORIGENIC IMMUNE INFILTRATES IN THE COLON AND GASTRIC ADENOCARCINOMA MICROENVIRONMENTS Wu, Xiangyan	CB 18
IDENTIFICATION OF IMMUNE SUBSETS MARKERS, CCL22, ZNF366, AND GPR114, AS CANDIDATE REGULATORS OF GENOMIC INSTABILITY IN HUMAN LUNG ADENOCARCINOMA Yamada, Hiroshi	CB 19
DEPTH-RESOLVED IMAGING OF BLADDER TUMOR USING OPTICAL COHERENCE TOMOGRAPHY AND FLUORESCENCE LAMINAR OPTICAL TOMOGRAPHY Yan, Feng	CT 57
ACSS2 PROMOTES PANCREATIC CANCER CELLS SURVIVE NUTRIENT DEFICIENCY BY UPREGULATING ZIP4 Zhou, Zhijun	CB 20
CHALLENGING CLINICAL NUTRITION ASSUMPTIONS: HIGHER BODY WEIGHT PREDICTS LOWER PRE-OP PROTEIN INTAKE BEFORE PANCREATICODUODENECTOMY Zhou, Yong	CPC 41

BRG1 (SMARC4) INFLUENCES THE RESPONSE TO EGFR INHIBITORS IN LUNG CANCER

Authors: Rebaz Ahmed[1,5], Akhil Srivastava[1,4], Narsireddy Amreddy[1,4], Meghna Mehta[2,4], Janani Panneerselvam[1,4], Rodrigo Orlandini de Castro[6], William Berry[3,5], Roberto Jose Pezza[4,5,6], Anupama Munshi[2,4], Rajagopal Ramesh[1,4,5]

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Background: Epidermal growth factor receptor (EGFR) is overexpressed in several human cancers including non-small cell lung cancer (NSCLC) and has become an important molecular target for therapy. The occurrence of gain of function via activating mutations in the intracellular kinase domain (IKD) of EGFR provides signaling cues for cell proliferation, differentiation, and survival. Gefitinib (GEF) is an orally available, selective EGFR-tyrosine kinase inhibitor (TKI) that results in clinical benefit in NSCLC patients with EGFR mutations, but not in majority of NSCLC patients with wild-type EGFR (wt-EGFR), implying the existence of unexplored mechanisms that contribute to resistance to GEF. Treatment with GEF over a period of time results in drug resistance thereby leading to treatment failure. Recent studies indicate a role for BRG1 and other subunits of large SWI/SNF complex in modulating the response to anticancer therapies including TKIs. However, little is known whether BRG1 status influences the response to EGFR-TKIs. In the present study we therefore investigated how BRG1 influences the response to EGFR TKI in lung cancer.

Methods: NSCLC cells A549 (mt-BRG1, wt-EGFR) and H358 (wt-BRG1, wt-EGFR) tested for sensitivity to GEF (0.5, 1, and 2 µm) by performing cell viability assay at 24 hours. Stable H358-BRG1-KO and A549-BRG1-overexpression cells were created followed by GEF-treatment at 24 hours. Changes in phosphorylated-EGFR-(Tyr1068), EGFR and BRG1 expression in the GEF-treated cells were examined by western blot analysis.

Results: Results showed that A549 cells were relatively resistant (94.48%, 84.40% and 82.46% viability at 0.5, 1, and 2 µm GEF, respectively) than H358 cells (88.5%, 74.88% and 57.66% viability at 0.5, 1, and 2 µm GEF, respectively) towards GEF-treatment. Molecular studies showed upregulation of BRG1 with concomitant reduction in EGFR in GEF-treated-H358 cells. In contrast, mt-BRG1-A549 cells showed no change in EGFR expression levels upon GEF-treatment. H358-BRG1-KO cells exhibited resistance to all the concentrations of GEF 24 hours. Whereas overexpression of BRG1 in mt-BRG1-A549 showed trend towards sensitivity all the concentrations of GEF..

Conclusion: The upregulation of BRG1 in GEF-treated-H358 cells suggests possible molecular interaction between EGFR and BRG1 and that BRG1 possibly influences resistance to EGFR-TKIs. Demonstrating the role of BRG1 in EGFR-TKIs resistance allows testing of new combinatorial treatment strategies targeting both BRG1 and EGFR.

Keywords: Non-small cell lung cancer, epithelial growth factor receptor, tyrosine kinase inhibitors, drug resistance, molecular targeted therapy, SWI/SNF complex, BRG1

A NOVEL T-ALL TUMOR SUPRESSOR - OSR2

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Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, representing >25% of all cancers in children 0-14 years. Despite major advancements in pediatric ALL treatment, it remains the second most lethal childhood cancer, accounting for ~25% of deaths. The two types of ALL are precursor-B or B-ALL and precursor-T or T-ALL, and these are defined by distinct molecular landscapes. Of the two types, T-ALL comprises about 15% and 25% of pediatric and adult cases respectively, and is historically considered more aggressive and treatment-resistant, with inferior prognosis. In the precision medicine era, it is imperative to identify genetic alterations and aberrant gene expression patterns, to not only to better understand tumor biology, but also to improve treatment outcomes by developing new targeted therapies.

In this study, we are investigating a novel transcription factor, odd-skipped related transcription factor 2 (OSR2), which we hypothesize is a putative T-ALL tumor suppressor. To do this, we are using a zebrafish T-ALL model that expresses transgenic human MYC (hMYC) regulated by a lymphoblast-specific promoter, rag2. Prior work in zebrafish and human T-ALL found low levels of OSR2 expression in ~95% of T-ALL tested. Based on these data, we then used RNA-seq to analyze 10 hMYC zebrafish T-ALL, which confirmed low-to-absent osr2 expression in all 10 T-ALL, compared to wild-type (WT) T cells. We further confirmed decreased osr2 expression by qRT-PCR of 6 additional T-ALL compared to WT thymocytes. We hypothesized that, as a putative tumor suppressor, diminished Osr2 function might increase T-ALL incidence and shorten latency. To test this, we obtained osr2-mutant fish and bred these to rag2:hMYC transgenic animals to create three lines: heterozygous osr2-mutant (osr2het) fish, heterozygous hMYC (hMYC het) fish, and compound-heterozygote (osr2het;hMYChet) fish. We then screened each genotype for T-ALL incidence by serial fluorescence microscopy, and confirmed T-ALL by fluorescence-based flow cytometry. By 7 months, we found 9/18 (50%) of double-heterozygous fish developed T-ALL, compared to 0/7 hMYChet fish; osr2het fish also did not develop T-ALL. Together, our findings suggest osr2 allelic loss accelerates MYC-driven T-ALL, supporting our hypothesis that osr2 is a T-ALL tumor suppressor.

CONFINED SPACE MIGRATION CAN FACILITATE THERAPY RESISTANCE AND GENE EXPRESSION CHANGES IN GLIOBLASTOMA MULTIFORME

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Glioblastoma Multiforme (GBM) is the most common and highly aggressive brain cancer in adults. GBM cells diffusely migrate along brain white matter tracts in linear confined spaces along axons. These migrating cells survive initial therapies and lead to tumor recurrence, often with increased aggressiveness and treatment resistance. The consequence of Linear Confined Space Migration (LCSM) in treatment resistance is largely unknown. Here, we use a combination of microfluidics (5 µM wide channels in PDMS block) emulating linear white matter tracts in the brain and standard molecular analysis to investigate LCSM cells compared to Standard Monolayer Culture cells (SMCs) for the mechanism of drug resistance and to devise a better treatment strategy for GBM. We show that LCSM cells are more resistant to chemotherapy (Temozolomide and Doxorubicin) than SMC cells. LCSM cells demonstrated enhanced drug efflux compared to SMC cells indicating the activation of drug efflux pumps. Protein expression analysis indicated that ABC drug efflux transporters (ABCB1, ABCC1, ABCG2) were enhanced at varying levels in LCSM cells compared to SMCs in different GBM cell lines. Inhibition of ABC transporters based drug efflux using an ABCs/ABCG2 inhibitor Ko143 resulted in enhanced cell death by chemotherapy, suggesting that the resistance in LCSM, at least in part, is conferred by ABCG2 or other efflux transporters. In addition, CD133 (a marker of treatment resistant stem cell population in GBM) and AQP4 (Aquaporin 4; pro-migratory marker in GBM) were also enhanced in LCSM compared to SMC suggesting their possible roles in treatment resistance. In conclusion, our preliminary studies reveal that the enhanced expression of ABC transporters, prominently ABCG2, might be responsible for enhanced drug efflux and low therapeutic sensitivity in GBM-LCSM cells. However, more complex mechanisms might be involved in LCSM treatment resistance as indicated by increased expression of AQP4 and CD133, and differential expression of other genes which are currently under investigation.

CIGARETTE SMOKE INDUCES GOBLET CELL METAPLASIA IN HUMAN AIRWAY EPITHELIAL CELLS IN A NOTCH-DEPENDENT MANNER

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Introduction. Chronic obstructive pulmonary disease (COPD) is the 4th leading cause of death in the US and is caused primarily by cigarette smoking, which is also the leading risk factor for lung cancer development. Compared to smokers without COPD, patients with COPD have a two- to-fivefold greater risk of developing lung cancer and a poorer outcome following diagnosis and treatment. Goblet cell metaplasia (GCM) is an epithelial remodeling phenotype characterized by increased numbers of mucus-producing ("goblet") secretory cells. Excess mucus production leads to airway obstruction and contributes significantly to the pathophysiology of COPD. Therefore, identifying the mechanisms of how cigarette smoke exposure induces GCM may provide potential targets to develop therapeutic strategies to suppress COPD-associated GCM and increase the survival of COPD patients with lung cancer. The Notch signaling pathway plays a crucial role in regulating differentiation of the airway epithelium. The objective of this study was to determine whether Notch signaling regulates the induction of GCM in response to cigarette smoke exposure. **Methods.** Primary normal human bronchial epithelial (NHBE) cells (n=4,Lonza) were differentiated in vitro by air-liquid interface (ALI) culture for 28 days generating a pseudostratified epithelium consisting of basal, ciliated and secretory (Club and goblet) cells. The differentiated epithelium was exposed to cigarette smoke extract (CSE) and/or DBZ (⍺-secretase/NOTCH inhibitor) for 7 days. The effect of CSE on cell differentiation and Notch signaling was evaluated by RNA-sequencing, qPCR, Western blotting and histological staining. **Results.** Exposure of the differentiated airway epithelium to non-toxic concentrations of CSE (0.5% and 2.5%) resulted in an oxidative stress response (e.g. CYP1A1 induction) and structural changes in the epithelium. CSE exposure significantly increased goblet (MUC5AC+) cell numbers, with a corresponding significant decrease in the numbers of non-mucus producing Club (SCGB1A1+) cells, characteristic of GCM. Development of CSE-mediated GCM correlated with increased protein levels of activated NOTCH3 receptor but no change in NOTCH1 and 2. In addition, treatment of cells with the Notch signaling inhibitor DBZ during CSE exposure suppressed GCM. **Conclusion.** In vitro exposure of the airway epithelium to CSE induces GCM in a Notch-dependent manner. Therefore, targeting the Notch pathway may be a viable strategy to suppress GCM in smokers and patients with COPD.

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SHetA2 INCREASES THE ACTIVITY OF PALBOCICLIB IN CERVICAL CANCER IN VITRO AND IN VIVO

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Introduction: Standard of care therapies for cervical cancer are harmful to normal cells and cause many side effects. New, less toxic treatments are needed in order to avoid these toxic effects. We are currently studying a promising low-toxicity drug, SHetA2. SHetA2 is a flexible heteroarotinoid that induces apoptosis and G1 cell cycle arrest in cancer cells, but only induces G1 cell cycle arrest in healthy cells. Part of the mechanism of SHetA2 is its degradation of cyclin D1. Cyclin D1 forms a complex with CDK 4/6 and is important for G1 progression. Therefore, we combined SHetA2 with palbociclib. Palbociclib is an FDA approved CDK 4/6 inhibitor that is currently used in the treatment of hormone positive breast cancers and is currently in clinical trials for the treatment of ovarian cancer. Therefore, we hypothesized that SHetA2 and palbociclib would synergistically inhibit growth of cervical cancer in vitro and in cervical cancer cell- derived xenograft tumors.

Methods: The effects of SHetA2 and palbociclib alone and in combination were tested on cervical cancer cell lines using the MTT assay. Synergy was evaluated in cervical cancer cell lines by treating the cells with the drugs alone and in combination, then plotting their effects in an isobologram. Protein expression of phosphorylated Rb, and cleaved PARP were measured using western blot. An athymic nude mouse model was utilized to test the SHetA2/palbociclib combination in vivo. Mice were treated every day for 24 days with control solvent, 60mg/kg SHetA2, 100mg/kg palbociclib, or in combination. Differences in tumor growth inhibition between the groups were analyzed using repeated measure one-way ANOVA with multiple comparosions post-hoc analysis. Tumors were evaluated by immunohistochemistry and stained with CD31 and cyclin D1 antibodies.

Results: The drug combination consistently demonstrated synergistic activity in three cervical cell lines (CI < 0.5), with strong synergistic (CI < 0.1) activity in two cell lines. There was a consistent increase in cleaved PARP expression and reduction in Rb phosphorylation in the combination group in comparison to all other groups. When compared to control, all treatment groups significantly reduced SiHa xenograft tumor growth (p< 0.05). In post-hoc analysis, the growth inhibition in the combination group was significantly greater compared to the palbociclib only group (p=0.0127). In comparison to tumors in the control group, tumors in the combination treatment group exhibited dramatic reduction of cyclin D1 and angiogenesis.

Conclusions: The drug combination was synergistic in vitro and significantly effective in vivo. The mechanism of synergy appears to involve induction of apoptosis and reduction of cyclin D1, phosphorylated Rb, and angiogenesis.

TOBACCO USE IN LAO PEOPLE'S DEMOCRATIC REPUBLIC

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ABSTRACT

Background: Tobacco use is a burden for Lao People's Democratic Republic (Lao PDR). However, no published report has examined sociodemographic characteristics of tobacco users in Lao PDR to inform appropriate policies and prevention strategies.

Objective: This presentation highlights tobacco uses by sociodemographic characteristics in Lao PDR.

Methods: Data for analyses were from the most recent Lao National Adult Tobacco Survey in 2015, which included a nationally representative sample of 7,562 people aged ≥15 years. Participants were recruited through a stratified 2-stage cluster sampling approach in 18 provinces. All analyses were weighted.

Results: The results showed that 32.4% of Lao people aged ≥15 years were current tobacco users (51.2% in men and 15.4% in women). The prevalence of smoking any tobacco products was 27.9% (50.8% in men, and 7.1% in women). Cigarette smoking accounted for approximately 95% of all tobacco use in men. Tobacco chewing, including betel quid, was common in women (9.1% among the general population, 60% among all female tobacco users, and prevalence ratio=16.3 when compared with men). Current tobacco use was strongly associated with older ages and lower education levels (P-values <0.001). There were interactions between sex, education level, and income associated with tobacco use; specifically, women were more likely to have a lower education level and lower income than men, and these groups of women were more likely to use tobacco. Most smokers (80%) had never received advice to quit smoking from a healthcare provider. Less than 5% were former smokers (i.e., already quitted smoking) and less than 5% of current smokers ever made an attempt to quit. Most current smokers (88.4%) also believed that smoking causes bronchitis, lung cancer, or heart diseases, and this rate was not statistically different from that in non-smokers.

Conclusions: Tobacco use prevalence in Lao PDR was among the highest in the region. There were variations in types and prevalence of tobacco use across sociodemographic subpopulations. The Lao government should continue current national tobacco control efforts and implement additional proven strategies to reduce tobacco use. Being aware of harmful health effects of tobacco use is not sufficient to help smokers quit. Comprehensive tobacco cessation treatments, including a pharmacological component (e.g., nicotine replacement therapy) and behavioral intervention, may be necessary to advance smoking cessation rates.

Keywords: tobacco use, cigarette smoking, tobacco cessation treatment, Lao People's Democratic Republic.

MECHANISMS OF RESISTANCE TO THE ALLOSTERIC SHP2 INHIBITOR RMC-4550

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SHP2 is a protein tyrosine phosphatase (PTP) encoded by the PTPN11 gene. Previous studies by us and others have shown that SHP2 mediates oncogenic signaling and that SHP2 is required for tumor growth. Importantly, while SHP2 mediates RAS activation, tumors with KRAS mutations still depends on SHP2 for tumor growth. Recently, allosteric SHP2 inhibitors were developed and progressed rapidly to human clinical trials. However, SHP2 inhibition often could not completely kills cancer cells in cell cultures. To determine the mechanism of resistance to SHP2 inhibition, we cultured the SHP2 inhibitor sensitive, KRAS(G12C)-mutant H358 lung adenocarcinoma cells with the SHP2 inhibitor RMC-4550. The SHP2 inhibitor-resistant subpopulations of cells were enriched for four passages of continuing cultures with RMC-4550. We then performed biochemical and transcriptome analyses to compare the differences between the parental cells (H), RMC-4550-enriched cells under continuing treatment of RMC-4550 (R), and RMC-4550-enriched cells after removal of RMC-4550 (RN). Results of biochemical analyses showed the activation of the ErbB family of growth factor receptors and signaling pathways in the RMC-4550-enriched cell populations. Results of the RNA-seq experiment showed increased expression of extracellular proteins and several growth factor receptors and ligands. These results suggest that increased production of extracellular matrix proteins and reactivation of growth factor receptor signaling confer resistance to the SHP2 inhibitor.

QUANTIFICATION OF DNA DAMAGE ON HPRT AS A BIOMARKER OF CANCER RISK

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Background: The prevention of cancer and the development of more effective strategies to detect cancer precursor and early-stage cancers remain critical goals. It has been estimated that 50% to 60% of cancers could be prevented if known strategies were optimally used. Cancer risk is not uniform, but varies based on age, genetic susceptibility, exposures, existence of preneoplastic conditions across the population. The DNA is constantly damaged by exogenous and endogenous sources. DNA repair mechanisms maintain the integrity of the genome. DNA damage has emerged as a major culprit in tumorigenesis and progression. There are numerous strategies with inherent advantages and disadvantages that may be used for the evaluation of DNA damage and repair. We have developed a novel and highly sensitive primer-anchored DNA damage detection assay (PADDA) to map and quantify DNA damage in p53, the most frequently mutated gene in human cancer. Recently, we have extended this assay to HPRT (hypoxanthine-guanine phosphoribosyltransferase), the gene most frequently analyzed in DNA damage studies.

Aim: (1) To quantify the amount of DNA damage in HPRT in peripheral blood cells of never-smokers, smokers, and secondhand smokers. (2) To determine whether cancer patients have higher levels of DNA damage than non-cancer patients.

Methods: The assay, PADDA was used on a high-throughput setting to quantify DNA damage (q-PADDA) on the HPRT gene. DNA was extracted and damage was quantified by q-PADDA in peripheral blood cells collected from non-cancer patients [never-smokers (n=28), tobacco smokers (n=25), secondhand smokers (n=18)], and cancer patients (n=66). Pairwise comparisons in DNA damage among the diverse groups were performed using the Tukey's adjustment in a one-way ANOVA model. Linear regression models were also used to test difference in DNA damage between cancer and non-cancer groups.

Results: Never-smokers, tobacco smokers, and secondhand smokers had similar age distribution. In non-cancer patients, the amount of DNA damage in the HPRT gene in smokers was significantly higher than in non-smokers (p=0.01). Secondhand smoker also showed higher levels of DNA damage than never-smokers but this difference did not reach significance. Among cancer patients (n=66) smokers (n=29) also showed the highest levels of DNA damage (p=0.03).

Conclusion: Our preliminary data documented PADDA's ability to quantify DNA damage on HPRT gene. Damage was significantly higher in smokers than never-smokers. Also, smokers with cancer showed a higher level of DNA damage than others. Application of this assay to large population has a major potential to establish biomarkers of susceptibility to tobacco-induced disease, which can guide preventive and diagnostic strategies.

RNAi SEED-BASED APPROACH TO TARGET ANDROGEN SIGNALING NETWORKS TO INDUCE CELL DEATH IN PROSTATE CANCER CELLS

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Prostate cancer (PCa) accounts for approximately 10% of cancer related mortalities in men in the USA. The dependence of PCa cells on androgen signaling is often exploited clinically with androgen deprivation therapy (ADT); however, the majority of patients eventually progress to therapeutic resistance, termed castration resistant PCa (CRPC), which is incurable and frequently fatal. In approximately 70% of cases, CRPC cells are able to sustain androgen signaling in the presence of castrate androgen levels. In these cases, resistance is often driven by amplification, mutation, alternative splicing of the AR or amplification and overexpression of AR coregulatory genes. The direct targeting of AR with small molecular inhibitors has yet to produce durable positive outcomes in metastatic CRPC, and the high number and potential functional redundancies of certain AR coregulators present challenges in targeting these proteins. Targeting the AR in combination with multiple AR coregulators may have efficacy; however, clinically successful combinations have not yet been identified.

In this study, we describe a process using an RNAi seed-based approach to simultaneously target and downregulate AR and numerous AR coregulators, as well as other survival pathways, in PCa cells. We discovered that multiple shRNAs targeting the gene TMEFF2 lowered the expression of androgen responsive genes (ARGs), reduced AR protein expression and induced cell death in PCa cell lines, including a CRPC cell line expressing a clinically relevant constitutively active AR spliced isoform, AR variant 7. Lack of toxicity in CRISPR-mediated TMEFF2 knockout PCa cells, as well as observed toxicity induced by TMEFF2-targeted shRNAs in TMEFF2-negative cell lines, led us to hypothesize that the toxicity was driven by a potent off-target mechanism. RNA-seq and gene set enrichment analyses indicated that ARG sets were the only gene sets (Msig Database) consistently downregulated by all target shRNAs tested. In addition, AR, AR coregulators and essential survival genes were found to be downregulated by target shRNAs in a manner that was significantly associated with the presence of sequences complementary to the 6mer seed sequences in the 3' UTR of said genes. Experiments using CRPC mouse xenografts demonstrated that tumor growth was essentially abolished by TMEFF2 targeted shRNA expression. We propose that this RNAi seed-based approach to target androgen signaling presents a promising future therapeutic strategy for the treatment of CRPC.

THE IMPACT OF SURGICAL DELAY ON BREAST CANCER RECURRENCE: A SEER-MEDICARE ANALYSIS

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Breast cancer is the most commonly diagnosed malignancy among women in the United States with over 260,000 expected new cases in 2019. Over 80% of breast cancer are diagnosed at an early stage, yet the recurrence rates remain as high as 13-35%. Despite improvements in 5-year survival, women with early-stage breast cancer still face a significant risk of recurrence. Recent studies have found the interval between definitive diagnosis and surgical resection of breast tumor (time to surgery; TTS) is increasing and such delays in surgery are potentially associated with negative survival outcomes. However, it is unknown whether prolonged TTS is associated with disease recurrence in women with early stage breast cancer.

The Surveillance, Epidemiology and End Results (SEER)-Medicare Database is the largest population-based database of oncology patients in the United States, de-identified and linked to include Medicare claims on SEER patients. Using a retrospective cohort from the SEER-Medicare Database who were diagnosed with early stage invasive breast cancer between January 1, 2003 and December 31, 2013 and received surgery as their first treatment, we will analyze annual trends of TTS as well as the effect of TTS on breast cancer recurrence. An adjusted Cox proportional hazards regression model will be used to analyze the relationship between treated recurrence and TTS .

INVESTIGATING THE GENOMIC STABILITY OF INDUCED PLURIPOTENT STEM CELLS IN LONG TERM CULTURE

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Since their creation in 2007, induced pluripotent stem cells (iPSCs) have offered great promise in the field of regenerative medicine. By utilizing four key transcription factors, Oct-4, Sox2, Klf4, and c-Myc, the Yamanaka group was able to induce differentiated somatic cells to a pluripotent state. By reprogramming a patient's own cells, immunological rejection can be avoided during transplantation. Though iPSCs have much promise, they are still fraught with pitfalls which must be overcome- namely the accumulation of genetic aberrations which can occur in culture. During development and expansion iPS cells must be grown in artificial culture conditions for extend periods of time, which can introduce many types of genetic abnormalities. These alterations can range from aneuploidy to subchromosomal changes, characteristics often associated with cancer cells. In order to gain new insight into the nature of these genetic aberrations, two iPS cell lines were grown in concert and examined periodically over the course of 50 passages.

While the iPSCs were being cultured, their genomic integrity was examined periodically through the use of the Bionano Genomics Saphyr, an optical mapping instrument. The Saphyr is able to identify structural variations across the entire genome ranging from 500 base pairs to megabase pairs in length. Notably, the instrument is able to identify inversions and balanced translocations which do not produce copy number changes. Using this instrument, we were able to detect hundreds of structural variations not present in the general population. In addition to subchromosomal changes, analysis via the Saphyr detected a third copy of chromosome 12 in a later passage of one of the two iPSC line populations. This trisomy was later confirmed via chromosome spreads, which also provided a range of passages during which time the aberration entered the cell population. In addition to examining the iPSC's genomic integrity, the doubling time of each cell line was determined with every passage, providing additional insight into the effects of long-term culture on iPSC behavior.

PROGNOSTIC FACTORS FOR RESPONSE TO CHEMOTHERAPY IN PATIENTS WITH ADVANCED OR RECURRENT ENDOMETRIAL CANCER

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Objectives: To identify prognostic factors and develop a model predictive of response to chemotherapy amongst patients with advanced or recurrent endometrial cancer (EC).

Methods: In this multi-institutional retrospective study, 155 patients with advanced or recurrent EC who received systemic chemotherapy were evaluated for baseline clinical characteristics. Prognostic factors predictive of response were identified using a Logistic regression model. Adjusted Cox proportional hazards models using a backwards selection procedure were utilized to assess how covariates were associated with progression free (PFS) and overall survival (OS) in the presence of other variables. A predictive model was developed.

Results: Multivariable analysis identified 4 factors (African-American, type II EC, progressive disease following initial treatment, and multiple recurrent lesions) independently prognostic of poor response. Notably, adjuvant chemotherapy with initial radiation therapy did not affect prognosis. An additional 4 factors known to have prognostic significance (age ≥70 years, stage 3/4, presence of LVSI on uterine specimen, and depth of invasion ≥50%) were also included. A simple prognostic index was derived based on the total number of risk factors and patients were classified into three risk groups: low risk (0-2 factors), mid risk (3-5 factors), and high-risk (6-8 factors). Patients in the low-risk group experienced an overall response rate (ORR) of 96% to systemic chemotherapy with median PFS of 15.2 months and median OS of 29.6 months. Whereas patients in the high-risk group experienced an ORR of 50% to systemic chemotherapy with a median PFS of 12.3 months and median OS of 19.2 months.

Conclusions: A simple index based on eight prognostic factors may have utility in clinical practice to identify the women with advanced or recurrent EC who are not likely to respond to systemic chemotherapy. External validation of this predictive model is needed. Receipt of a prior radiosensitizer does not adversely affect response to subsequent chemotherapy following recurrence and should not be an exclusion factor for clinical trials evaluating systemic therapies.

CLEAR CELL CARCINOMA OF THE OVARY TREATED WITH PEPTIDE-TARGETED MESOPOROUS SILICA NANOPARTICLES

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Purpose: Clear cell carcinoma of the ovary (CCCO) is the most lethal of all gynecological tumors with a 5-year survival rate estimated at 40%. Advanced-stage CCCO lethality is attributed to its chemoresistant nature, limiting the effectiveness of therapeutics. Rapid identification and treatment of CCCO is necessary to reduce patient mortality rates. Given their biocompatibility and loading potential, wormhole mesoporous silica nanoparticles (MSNs) can likely achieve these goals. This study demonstrates the effectiveness of MSNs conjugated with a CCCO-specific ligand in identifying CCCO presence through pH-specific release of dye molecules.

Methods: Using hexadecyltrimethylammonium bromide (CTAB) as the molecular scaffold, MSNs were synthesized using tetramethyl orthosilicate (TMOS). CTAB scaffold removal through acid dialysis preceded coating the particles with chitosan, a pH-sensitive gatekeeper. Particles were characterized using transmission electron microscopy (TEM), dynamic light scattering (DLS), zeta potential, and UV-vis spectroscopy. Chitosan-coated TMOS MSNs were loaded with propidium iodide (PI) or IR-780 dye. Dye release was evaluated using UV-vis spectroscopy. To improve tumor specificity, chitosan-coated TMOS MSNs were conjugated to a pH-(low)-insertion-peptide (pHLIP), V7. In vitro CCCO cells (ES-2) were plated in pH 7.4, 6.8, and 6.6 PBS solutions and treated with dye-containing V7-conjugated MSNs (V7-CMSNs) or dye-containing non-targeted MSNs. Particle uptake in cells was determined using near-infrared fluorescence imaging.

Results: TMOS MSN diameters were 33 nm with TEM and 35 nm with DLS with polydispersity index of <0.13. Chitosan-conjugated dye-loaded particles demonstrated pH-specific dye release with 2X higher release at pH 6.6 compared to pH 6.8 and 10X higher than pH 7.4 over 6 h. V7-CMSNs particles demonstrated increased tumor-specific ES-2 cell uptake compared to non-targeted MSNs.

Conclusions: Insertion peptide V7 is effective for targeting CCCO cells when conjugated with TMOS MSNs, suggesting a tumor-specific pH-responsive nanoparticle suitable as a diagnostic or drug delivery vehicle.

ECIG AEROSOL ALTERS ANTI-OXIDANT AND DETOXIFYING ENZYME EXPRESSION LEVELS IN THE HUMAN ORAL EPITHELIAL CELLS

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Background: Last decade, there has been an increasing interest in the use of electronic cigarette (e-cig) among the youths. E-cigs are promoted as a safer alternative to tobacco cigarettes, but the long term health effects of e-cigs are unknown. E-cig aerosols contain harmful and potentially harmful substances, i.e., nicotine, ultrafine particles, flavoring agents, carbonyl compound, heavy metals, and carcinogens. In addition to containing reactive oxygen species (ROS), e-cig aerosols can also increase the cellular ROS production potentially leading to further alterations in the antioxidant system and its regulators. A recent in-vitro study from our laboratory showed that e-cigs aerosols can suppress the cellular antioxidant defenses and induced oxidative DNA damage in human oral epithelial cells. The effects of e-cig aerosols on antioxidant and detoxifying enzymes and its regulators are unknown.

Aims: To investigate whether exposure to EC aerosol extracts alters the expression of antioxidant and detoxifying enzymes in human oral epithelial cells.

Methods: Human oral epithelial cancer (SCC1) and non-cancer (POE9n) cell lines were exposed every other day for 2 weeks to e-cig aerosol. E-cig aerosol were prepared from two distinct e-cig brands (18 mg/ml of nicotine; tobacco flavor). Standard tobacco extracts (mainstream smoke MS) were used as positive control. Gene and protein expression were quantified by RT-PCR and Western blotting respectively. Data were analyzed by Student's t-test and ANOVA.

Results: Exposure to e-cig aerosol, but not to MS smoke, led to a decrease in NRF2 and SOD2 mRNA expression in both cell lines. A significant decrease in protein expression was also observed for NRF2 protein after exposure to e-cig aerosol. A significant increase in CYP1B1 was observed after exposure to e-cig aerosol and MS smoke.

Conclusion: E-cig aerosol exposure decreases the expression of NRF2 a major regulator of the antioxidant response. This might put the cell under additional oxidative stress which can have major biological implications. E-cig aerosol exposure increases the expression of CYP1B1, a protein with a key role in the metabolism of tobacco pro-carcinogens. Overall, our study suggests that e-cig aerosol not only carries high levels of ROS, but also alters the cellular detoxification and antioxidant system leading to a higher oxidative stress status that would be anticipated.

PREVALENCE AND ASSOCIATIONS OF PELVIC FLOOR DYSFUNCTION IN CERVICAL CANCER SURVIVORS

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Objective: Pelvic floor dysfunction (PFD) has a large impact on the quality of the life among cervical cancer patients. Previous studies have showed an increased incidence of PFD in gynecologic malignancies, our aim is to specifically look at cervical cancer survivors.

Methods: This study was conducted at a large academic cancer center. Selection criteria included women aged older than 18 years with a history of cervical cancer of any stage who were being seen in the Gynecology Oncology Survivorship Clinic. An IRB approved survey was completed during routine follow up. Composite impact scores for gastrointestinal (GI), urinary symptoms and pelvic pain over the last 7 days were compiled. Demographic, clinical and treatment data was collected and tested for association with reported PFD symptoms.

Results: A total of 98 participants were included. A high prevalence of pretreatment PFD in cervical cancer survivors was observed, 49.0% (48/98). A total of 39 (39.8%) of participants reported constipation and 21 (21.4%) reported frequent diarrhea. Increasing BMI was found to be associated with constipation, p=0.04. 59.2% (58/98) reported urinary urgency, 60.0% (60/98) reported urinary frequency, with 36.7% (36/98) with symptoms starting following treatment. Over half 53.7% (32/67) of the patients that were sexually active reported dyspareunia. Pelvic pain was reported to be 42.7% (41/96) with 9.4% (9/96) having frequent or almost constant pelvic pain. BMI, stage, parity and Charleson comorbidity index were tested for association with reported GI-, urinary- and pain- related PFD scores; only BMI was negatively associated with having a higher composite GI PFD score, p=0.02. Association with prior treatments were tested. Those (n=62) receiving radiation therapy (RT) vs those (n=33) who did not had significantly higher GI-related PFD composite score, p=0.03 and marginally significantly higher pain- and urinary-related composite scores, p=0.07 and 0.08, respectively. Surgery and RT was not significantly associated with higher composite PFD scores. RT was associated with increased depression and anxiety, p= 0.04 and 0.03 respectively.

Conclusion: Reported PFD is prevalent in patients with a history of cervical cancer both prior to treatment and ongoing severe symptoms are associated with prior radiation treatment independent of BMI and parity. Possible incorporation of screening for PFD pre and post treatment may aid in ability to offer appropriate treatments earlier in the process or potentially target high risk individuals for early interventions.

Table 1: Baseline Characteristic for PFD Study

Characteristic (N=98)	All
Age in years (median)	48.7 (range 25-98)
BMI in kg/m² (median)	29.6 (range 17-52)
Race	
White/Caucasian	70
Black/African American	7
Hispanic/Native American	11
Other	8
Parity	
No Pregnancies	14
1-2 Pregnancies	28
>2 Pregnancies	50
Radiation	
Yes	63
No	33
Surgery	
Yes	53
No	47
Tobacco Use	
Yes	52
No	45
Stage	
Ia1	10
Ia2	6
Ib1	36
Ib2	19
IIa1	2
IIa2	4
IIb	16
IIIb	8
IVb	0

ROLE OF MRTFS IN CANCER ASSOCIATED FIBROBLASTS IN METASTATIC COLORECTAL CANCER

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Treatment related costs due to colorectal cancer (CRC) in the United States are greater than 15 billion dollars per year, yet, CRC still has a nearly 40% mortality rate. More recent attention has focused on the non-transformed cells in the tumor microenvironment (TME), rather than the tumor cells. This TME is made up partly of cancer associated fibroblasts (CAFs), which are smooth muscle alpha actin (SMαA) positive cells that form in response to the tumor. SMαA is one of the most widely used markers to identify CAFs and increased expression is an indicator of poor survival in CRC patients. Moreover, it has been shown that CAFs have the ability to reorganize the extracellular matrix in a way that the cancer cells become capable of migrating away from the primary tumor in order to metastasize. MRTF-A and MRTF-B (MRTFs, collectively) are transcription factors that have been shown to promote the formation of myofibroblasts in response to changes in mechanical tension in the tissue they inhabit.

Our central hypothesis is that MRTFs are required for CAF formation and function which facilitates colon cancer metastasis. Our results show that MRTFs promote the transition of normal intestinal fibroblasts into CAFs. Conversely, depletion of MRTFs reverses the formation of CAFs by downregulating the expression of SMαA, SM22α and CTGF. Taken together, our data suggest that MRTFs are required for the expression of genes upregulated in CRC CAFs. Lastly, CAFs contribute to metastasis and resistance to cancer therapies, modulating them may help overcoming clinically refractory disease.

INVESTIGATION OF ANTI-CANCER DRUG RESISTANCE IN OVARIAN CANCER SPHEROIDS

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Ovarian cancer is the most lethal gynecological disorder with a survival rate of 47% within 5 years[1]. High fatality is due to early peritoneal dissemination and resistance to chemotherapy. This dissemination occurs through the formation of multicellular aggregates, called spheroids[2], comprised of single or clusters of detached cells from the tumor[3].Mesothelial adhesion of spheroids leads to the invasion of extracellular matrix[4]and subsequently spreading of the tumor to distant locations. Anti-cancer resistance is a well-known criterion when treating ovarian cancer and, in this project, we analyzed the anti-cancer drug resistance of epithelial ovarian cancer spheroids. We describe the ultra-low attachment mediated formation of epithelial ovarian cancer spheroids by using OVCAR-3, SKOV-3 and OVCAR-8 cell lines. OVCAR-8 cells had 8-fold increased IC50 concentration for anti-cancer drug paclitaxel compared to OVCAR-3 and SKOV-3 cells in monolayer and used to investigate whether monolayer resistance is preserved also in spheroids. Spheroid were initiated with different numbers of cells and monitored for their formation over 6 days and characterized in terms of projected surface area, diameter, solidity and circularity. At the end of 6 days, viability was assured by using Live/Dead assay. Then spheroids were tested for their drug resistance by using anti-cancer drug paclitaxel. Spheroid were found more resistant than their monolayer counterparts for all cell lines. Size of the spheroids influenced the effect of the drug. Future studies will include investigating the resistance in terms of spheroid size and certain gene expression analysis.

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THE EFFECT OF EXTRACELLULAR SELF-ASSEMBLY OF MMP-9 RESPONSIVE SUPRAMOLECULAR STRUCTURES ON OVARIAN CANCER CELLS

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Introduction

In the United States, nearly 25,000 women receive new diagnosis of ovarian cancer each year and only 30% of these cases are curable because of disseminating spheroids in the peritoneal cavity. Yet, current chemotherapeutic approaches are ineffective against spheroids due to their drug resistance and metastatic ability. MMP-9 (matrix metalloproteinase-9), an enzyme responsible for extracellular matrix degradation, causes ovarian cancer to have metastatic ability and constitute a target for treatment. We engineered self-assembling nanoparticles (NPs) which are composed of DSPE-PEG (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethyleneglycol)-2000])5,6), MMP-9 cleavable peptide domain and anionic/cationic peptide group. Upon cleavage in cancer microenvironment, NPs switched from spherical micelles to fibrous structure and formed self-supporting hydrogels through self-assembly of the anionic/cationic peptides. We proposed that this nanonetwork entrapped spheroids and resulted in cellular death due to nutrient starvation. Such treatment can prevent the spread of spheroids through abdomen.

ABNORMAL LYMPHOPOESIS PRECEDES THE ONSET OF ALL IN HMYC TRANSGENIC ZEBRAFISH

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Acute lymphoblastic leukemia (ALL) is an aggressive hematologic malignancy that afflicts children and adults. ALL develops as a clonal expansion of an early precursor cell of either the B or T lineage, depending upon the specific genetic aberrations that occur, and what lymphoblast lineage they occur in. Over 60% of ALL overexpress the myelocytomatosis (MYC) oncogene. Overexpressed MYC is known to drive leukemogenesis, but MYC alone is insufficient to transform normal lymphoblasts into malignant form. Additional genetic/epigenetic changes have been linked with MYC in other cancers. These genetic events have not yet been discovered in ALL. Zebrafish develop highly-penetrant MYC-driven ALL with short latency. Transgenic fish with murine or human MYC (mMyc, hMYC) driven by rag2 promoters have been studied extensively with respect to T-ALL, and recently also B-ALL. Our lab, uses double-transgenic rag2:hMYC, lck:eGFP fish, where T cells are GFPhi and B cells are GFPlo. Lymphocyte protein tyrosine kinase (lck), cell-specific fluorophore, was thought to be only expressed by T lymphocytes. However, we found that a B cell subpopulation, innate lymphoid (ILCs and NK cells) and even myeloid cells also express lck. Thus, we can use lck:eGFP fish (with or without hMYC) to study abnormal lymphopoiesis that precedes the onset of MYC-induced ALL. We hypothesize that MYC hyperactivity causes aberrant proliferation of lymphoblasts before their malignant transformation, setting the stage for additional genetic changes to develop ALL. Our data show that overexpressed MYC causes lymphoid hyperplasia of primary (thymus and marrow) and secondary (spleen) lymphoid organs in pre-leukemic stage. This include increase in thymic B cell, a rare and poorly-understood population in WT fish, and in humans. Our current efforts seek to identify the MYC-associated genes that drive the lymphoid hyperplasia to develop B- or T-ALL by transcriptomic analysis.

A MACHINE LEARNING APPROACH TO IDENTIFYING RESPONSE FATIGUE AND NON-COMPLIANCE IN ECOLOGICAL MOMENTARY ASSESSMENT

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Significance: Ecological momentary assessment (EMA) allows for a more granular understanding of the relationship between affect, socioenvironmental context, and smoking lapse. EMA involves frequent measurements in an individual's natural environment, reducing recall bias that is characteristic of self-report instruments. Yet, there is no gold standard method of validating EMA reports of momentary smoking. Lack of adherence to self-initiated event reporting and participant response fatigue (i.e., when the quality of the data provided begins to deteriorate in association with participant burden) can lead to misclassification of smoking lapse or abstinence. The purpose of this study is to use machine learning methods to identify response fatigue and predict non-compliance with EMA protocols.

Methods: Participants were adults from a clinic-based smoking cessation program. Participants were loaned smartphones and prompted to complete 5 EMAs each day from 1 week pre-quit to 4 weeks post-quit, and to self-initiate an EMA whenever they lapsed. EMAs evaluated mood, smoking urge, environmental context, and smoking lapses. Meta data from EMA reports (e.g., participant time in study, average time to complete each question, grade reading level, etc.) were used as potential indicators of participant engagement and response fatigue. Gradient boosted decision trees with k-fold cross validation were used to predict EMA completion and response time.

Results: A total of 29,618 scheduled EMAs and 8,582 participant-initiated EMAs were included for analysis. Participants completed 81.3% of all prompted EMAs. Predictive features included question type, number of times a question has been seen, order of questions, and participants' median response time. Final models, including practical suggestions for identifying response fatigue will be discussed.

Conclusion: Accurate identification of momentary smoking episodes and their context is crucial for the development of effective just-in-time adaptive interventions for smoking cessation. The methods discussed herein may be effective in identifying patterns of non-compliance and fatigue that can be used to refine future EMA study protocols.

MOHS MICROGRAPHIC SURGERY FOR SQUAMOID ECCRINE DUCTAL CARCINOMA: A CASE REPORT.

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Introduction

Squamoid eccrine ductal carcinoma (SEDC) is a rare variant of eccrine carcinoma that is clinically aggressive and has the propensity to metastasize. With clinical and pathological resemblance to squamous cell carcinoma (SCC), diagnosis of SEDC is often a challenge. Due to the rarity of the tumor and lack of data in the literature, there is no standardized recommendation for management of these malignancies.

Case Report

A 74-year-old Caucasian woman with a significant history of basal cell carcinomas and squamous cell carcinomas presented to the dermatology clinic with left nasal sidewall pain with no cutaneous changes. She had a history of SCC in the same location the previous year, which was treated with MMS. A recurrent SCC was suspected, and a CT scan of the head and neck was performed which was unremarkable. A punch biopsy in the area where she was having the pain revealed SEDC. Three additional punch biopsies were performed on the nose to determine the extent of the tumor; all three biopsies showed no evidence of malignancy. Mohs surgery was performed which resulted in a partial rhinectomy with significant extension onto the left cheek. The patient is currently receiving radiation therapy and awaiting a positron emission tomography scan. After completing radiation, the Mohs defect will be repaired with a paramedian forehead flap.

Discussion

SEDC is an uncommon variant of eccrine carcinoma. Clinically, these malignancies typically present as a solitary nodule or plaque with or without ulceration on the scalp, limbs, or torso of older individuals.[1]

Histologically, SEDC is composed of two layers of differentiation. The superficial layer tends to closely resemble that of a moderately well-differentiated SCC with the presence of superficial squamous cellular atypia, keratinous cyst formation, intercellular bridges, and squamous eddies.[1,2] In the deeper layer, eccrine ductal proliferation predominates with a poorly demarcated infiltrative pattern extending into the dermis and subcutaneous fat.[2] When utilizing superficial shave biopsy for diagnosis, the deeper layers that provide histological clues to diagnosing SEDC are often missed, therefore, SEDC is frequently misdiagnosed as SCC.[2]

Due to the aggressive nature of SEDC it is imperative that treatment is optimized to limit recurrence of disease. To date, there have been no randomized studies comparing treatment modalities of SEDC.[5] At an average of 30.9 months, the local recurrence rate of eccrine carcinomas is drastically reduced in MMS (0-5%) when compared to traditional wide excision (10-70%).[5] MMS is an effective method of treating SDEC with the consideration of adjuvant radiation therapy. PET scans should be used to assess local recurrence and metastasis. Close follow-up and post-surgical surveillance are necessary due to the aggressive nature of the tumor.

COMMON AND DISTINCT TRANSCRIPTOMIC FEATURES OF LUNG TUMORS INDUCED BY THE EGFR(L858R) AND KIF5B-RET PROTEIN TYROSINE KINASE ONCOGENES IN TRANSGENIC MICE

Xueqing Hu, Xuan Liu, Tao Shen, Qi Li, and Jie Wu

EGFR mutations and RET fusions are driver oncogenes in lung adenocarcinoma. We used doxycycline (Dox)-inducible CCSP-rtTA/tetO-EGFR(L858R) (CE) and CCSP-rtTA/tetO-KIF5B-RET (CKR) transgenic mice to model the EGFR mutant- and RET fusion-induced lung adenocarcinoma. Dox-induced CE mice had rapidly developed, extensive hyperplasia in the lungs, whereas Dox-induced lung tumors in CKR mice had extensive desmoplastic reaction. To compare the molecular features of these two mouse models of lung adenocarcinoma, we performed RNA-seq analyses of lung mRNA using the PE150 Illumina platform. Principal component analysis (PCA) clearly separated CKR, CE, and the control (Ctrl) samples. A total of 5925 differentially expressed genes (DEGs) were found between the CE and the Ctrl groups and 2821 DEGs were found between the CKR and the Ctrl groups (|Fold Change| ≥ 2, Adjust p value < 0.05). Interestingly, the EGFR ligands Ereg and Areg were the most significantly upregulated mRNA in the lungs of both CE and CKR. Among the most common significantly changes were upregulation of Lamc2, Krt8, and S100a14 mRNA, and the downregulation of Ednrb and Synm mRNA. Calca (calcitonin) and Ubd were among the most up-regulated genes in the lungs of CKR mice but not in the lungs of CE mice. Gene set enrichment analysis (GSEA) showed that the Notch and mTOR pathway genes were significantly enriched in both tumors. Pathway analyses showed that upregulated genes in the lungs of CE mice were functionally related to growth factor receptor signaling and mitosis, whereas upregulated genes in the lungs of CKR mice were characterized by cytokine signaling and extracellular matrix remodeling. These data reveal the involvement of EGFR ligands in lung tumor development of not only the EGFR mutant-driven but also the KIF5B-RET-driven lung tumors. While it remains to be validated, our observation that Calca was a top upregulated gene in the KIF5B-RET-induced lung tumors points to the possibility that calcitonin may be expanded as a serum marker for RET fusion-positive cancers beyond thyroid cancer.

COPPER-64 PET IMAGING OF THE CXCR4 CHEMOKINE RECEPTOR USING A CROSS-BRIDGED CYCLAM BIS-TETRAAZAMACROCYCLIC CHEMOKINE RECEPTOR ANTAGONIST

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Expression of the chemokine receptor CXCR4 plays an important role in cancer metastasis, autoimmune diseases, and during stem cell based repair processes after stroke and myocardial infarction. Previously reported PET imaging agents targeting CXCR4 suffer from either high non-specific uptake or only bind to the human form of the receptor. The objective of this study is to develop a copper-64 labelled small molecule PET agent for imaging both human and murine CXCR4 chemokine receptors to further translational research approaches in mouse models of cancer. Methods: Synthesis, radiochemistry, stability and radioligand binding assays were performed for the novel tracer [64Cu]CuCB-Bicyclam. In vivo dynamic PET studies were carried out on mice bearing U87 (CXCR4low) and U87.CXCR4 (CXCR4high) tumors. Biodistribution and receptor blocking studies were carried out on CD1-IGS immunocompetent mice. CXCR4 expression on tumor and liver disaggregates was confirmed using a combination of IHC, qPCR, FACS and WB. Results: [64Cu]CuCB-Bicyclam has a high affinity for the CXCR4 receptor (IC50 = 10 nM) and can be obtained from the parent chelator that has low affinity. In vitro and in vivo studies demonstrate specific uptake in CXCR4 expressing cells that can be blocked by >90% using a higher affinity antagonist, with limited uptake in non-CXCR4 expressing organs and high in vivo stability. The tracer was also able to selectively displace the CXCR4 antagonists AMD3100 and AMD3465 from the liver. Conclusions: The application of the tetraazamacrocyclic small molecule [64Cu]CuCB-Bicyclam is demonstrated as an imaging agent for both human and murine homologues of the CXCR4 receptor. It has high affinity and stability and showed suitable pharmacokinetic properties for preclinical research in syngeneic models. Funding was provided by the Daisy Appeal Charity (grant DAhul0211 and BPB fellowship) and by Yorkshire Cancer Research (HEND376).

CHEROKEE NATION HEALTH ANALYTICS CORE: LINKING CANCER REGISTRY AND ELECTRONIC MEDICAL RECORD DATA

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Background: Cherokee Nation and the University of Oklahoma Health Sciences Center (OUHSC) are collaborating on a National Institutes of Health-funded Native American Research Center for Health (NARCH) grant. The Cherokee Nation Cancer Registry (CNCR) is the first and only tribally-operated population-based Surveillance Epidemiology and End Results (SEER) cancer registry in the US. However, like most registries, CNCR lacks important behavioral risk factors, comorbidities, and detailed treatment and follow-up data. The goal of Cherokee Nation Health Analytics Core (CNHAC) is to build capacity for Cherokee Nation to conduct comprehensive cancer research. We plan to achieve this analytical capacity through training and data linkage between the CNCR and the Cherokee Nation electronic medical record (EMR) to examine health behaviors, disease status, and cancer outcomes among American Indian people with cancer living within the boundaries of Cherokee Nation reservation. Furthermore, another data linkage pilot research project on breast cancer patterns of care and outcomes by diabetes status among American Indians is also underway.

Methods: After obtaining approval from the Cherokee Nation Institutional Review Board and the Governing Board, the CNHAC staff conducted a data linkage between the CNCR and the Cherokee Nation electronic medical record (EMR). We have received exported data from the Cherokee Nation EMR vendor, Cerner, including identifiers for the data linkage and variables related to behavioral risk factors (i.e., smoking, body mass index), screening, diagnosis, and comorbidities. Diabetes-related data obtained for the pilot study include diabetes status, date of diabetes diagnosis, hemoglobin A1c, and diabetes therapy/medications.

Results: CNHAC staff identified 3,014 confirmed matches between the two data systems and are currently working to complete the data merge with the exported EMR data. We will report on the linkage process and provide descriptive characteristics comparing cancer cases who did and did not link to an EMR record. Characteristics will include linkage status by cancer site, year of diagnosis, age at diagnosis, and gender.

Discussion: As next steps, we plan to complete the linkage between CNCR and the EMR. In the future, we will validate linkages and data completeness. We will also conduct feasibility studies, including breast cancer patterns of care studies, to better understand what research questions can be addressed using the registry and EMR linkages. We will continue building a comprehensive data repository and capacity for research and explore other comorbidities and cancers to address health disparities.

END-OF-LIFE SERVICES IN TRIBAL COMMUNITIES

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Terminally ill American Indians/Alaska Natives (AIANs) are less likely to receive hospice and palliative care than other racial/ethnic groups, with fewer than 1/3 receiving these services compared to over 45% of EuroAmericans (Johnson 2013; NHPCO 2017). While some AIANs believe that End of Life (EoL) services will hasten their deaths (Colclough and Brown 2014), claims that Natives reject EoL services simply due to death taboos appear to be overgeneralizations. Extant studies point to barriers to access resulting from lack of financial resources and inadequate service infrastructure, especially in rural areas (Jervis, et al. 2002; Kitzes and Berger 2004; Kitzes and Domer 2004; Weech-Maldonado, et al. 2003). While these factors undoubtedly play a role in underutilization, our research suggests that other factors— e.g., lack of tribally based EoL programs and the cultural mismatches that occur when non-Native programs attempt to deliver hospice services to Native clients—discourage AIANs from engaging with these services. In this presentation, we report on results from a Stephenson Cancer Center funded nationwide telephone survey of the availability of EoL care across AIAN tribes. We also present findings from focus groups with local service providers on the challenges and successes they experienced in providing EoL care to their AI clients in one tribal community. Together, these findings add to our growing understanding of the factors that inhibit and facilitate EoL service utilization, and suggest possibilities for improving access

ER/PR + BREAST CANCER TREATMENT BY PH RESPONSIVE MESOPOROUS SILICA NANOPARTICLES

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Purpose: Breast cancer is the deadliest form of cancer for post-menopausal women. Traditionally, there are a wide variety of breast cancer diagnoses all with non-specific treatment options. Recent advances in genomics paved the way for a new method of diagnosing and treating breast cancer based on the hormone receptors and proteins present in the tumor. Many different therapeutic options have been discovered for targeted drug delivery in patients with HER2-Positive breast cancer, but there is a lack of targeted therapy options for patients presenting with alternative breast cancer diagnoses. Targeted nanotherapy has become an important step in the effort to create theranostic drug delivery vesicles. In this work, pH responsive nanoparticles are synthesized to target ER/PR + breast cancerous environments.

Methods: Tetramethyl orthosilicate (TMOS) was added to a hexadecyltrimethylammonium bromide (CTAB) scaffold at 80°C in order to synthesis mesoporous silica nanoparticles. A series of acid dialysis were conducted to remove the CTAB, creating wormhole like pores in the nanoparticles. The particles were loaded with IR780 dye and capped with chitosan to ensure the retention of the cargo at biological pH. Transmission Electron Microscopy (TEM), zeta potential, UV-Vis spectroscopy and dynamic light scattering (DLS) were used analyze the MSNs. Conjugation of these synthesized nanoparticles with V3 peptide allowed for the targeting of low pH environment consistent with ER/PR+ cell lines.

Results: TEM confirmed the 25nm size of the nanoparticles, while zeta potential and UV-Vis spectroscopy confirmed successful conjugation and coating. DLS measured the average size of the particle to be 33.09nm and the PDI to be 0.0858. The particles displayed peak release quantities at 6 hours and was 2x more affective at a pH of 6.5 than at pH of 7.4 and 6.5.

Conclusion: V3-TMOS-MSN are optimized for drug delivery and as a contrast agent for ER/PR + Breast Cancer.

NAPROXEN BLOCKS SPONTANEOUS LUNG ADENOMA PROGRESSION TO ADENOCARCINOMA IN KRAS-G12V MICE

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The aim of the present study was to investigate the effects of a non-steroidal anti-inflammatory drug (NSAID), naproxen, on a spontaneous mouse model of lung adenocarcinoma. Lung cancer is the most frequently diagnosed cancer and the primary cause of cancer-related deaths worldwide. Inflammation plays an important role in the development and progression of lung and several other cancers. The association between NSAID use and lung cancer risk suggests a beneficial effect on patients' lung cancer progression. Preventing lung cancer can help to significantly reduce cancer-related mortality. Compared with other NSAIDs, naproxen is relatively safer in terms of cardiovascular risk. Eight-week-old transgenic KrasG12V male and female mice (n=20) or littermate wild-type (n=5) mice were fed (AIN76A) diets containing naproxen (0 ppm or 400 ppm) in modified AIN76-A diet for 28 weeks. At 36 weeks of age, mice were euthanized. Lungs were collected and evaluated for lung tumor incidence and multiplicity, and were saved in formalin for histopathological identification of adenoma and adenocarcinoma. By 12 weeks of age, KrasG12V mice developed visible lung tumors that enlarged in size and progressed to adenocarcinoma by 24-36 weeks of age. Lung tumor incidence was observed in 100% of KrasG12V mice. Dietary administration of naproxen did not show any overt-toxicities. No significant changes were observed in body weight gain or any major organ's (liver, kidney, and pancreas) gross morphology or weight in mice fed with naproxen compared with mice fed control diet. Due to reduced tumor burden, lungs of the naproxen-fed mice weighed less (230.6± 12.2 mg, p=0.0192) (Mean±SEM) than those of the control group (384.0±68.1 mg). Importantly, mice fed control diet developed 19.8±0.96 total lung tumors (2.5±0.3 adenoma, 17.3±0.7 adenocarcinoma). The results suggest that naproxen inhibits total lung tumor formation by ~52% (9.4±0.85; p<0001) and adenocarcinoma by ~64% (6.1±0.6; p<0001), compared with control diet. However, we observed no significant difference in the number of adenomas in mice fed with control diet and mice fed naproxen diet. These data suggest that naproxen delays the progression of lung adenoma to adenocarcinoma. Biomarker analysis of lung tumors from mice exposed to naproxen showed significantly reduced tumor cell proliferation (PCNA, Cyclin D1) and increased apoptosis (p21, Caspase-3). These results support a chemopreventive role of naproxen in spontaneous-induced lung adenocarcinoma formation.

PHARMACOLOGICAL MODULATION OF INFLAMMATION AND P53 SIGNALING SYNERGIZE TO PREVENTS MUSCLE INVASIVE BLADDER CANCER IN-VIVO

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Bladder cancer (BC) is the second most common genitourinary cancer and a leading cause of death globally. Muscle invasive BC (MIBC) has high mortality (>85% patients) leading to death within 2 years of diagnosis, if untreated. Although new treatment options were approved recently, it is still very challenging and most expensive to manage. Preventing BC is highly desirable to reduce recurrence, mortality and improve quality of life. Inactivation of p53 signaling and chronic inflammation are frequent hallmarks of MIBC. In spite of the promising chemopreventive effects of non-steroidal anti-inflammatory agents (NSAIDs), their clinical translation is hampered due to side-effects associated with their chronic intake and higher doses. Here we investigated a combinatorial approach to modulate inflammation with NSAIDs (licofelone or NO-Naproxen) and p53 signaling pathways using CP-31398 (CP) for preventing MIBC bladder in-vivo. Transgenic UPII-SV40T mice developing spontaneous MIBC were generated and fed control or experimental diets containing the licofelone (150ppm), NO-naproxen (300 ppm), CP (150ppm) alone or in combination starting at early tumor stage (6 weeks age). After 34 weeks of agent administration, mice were euthanized and urinary bladders were evaluated. Control diet fed transgenic mice developed high grade, muscle invasive, urothelial transitional cell carcinoma (TCC) leading to 3-5 fold increase in bladder weights (140.2±9.8 mg Vs 27.3±0.8 mg; p<0.0001) and (34.2±0.8 mg vs 14.8±0.53 mg; p<0.0001) in males and females compared with wild type mice. These tumors had dysregulated cell cycle and inflammation markers similar to human tumors. Treatment with licofelone, NO-Naproxen or CP alone led to significant suppression of bladder tumor. While NSAIDs had significant inhibitory effect in males (65% - 78%; p<0.0001) and females (31% - 34%; p<0.01-p<0.0001) compared to control group, CP had strongest tumor growth suppressive effect (80%; p<0.0001 and 36%; p<0.0001) in both genders. CP had no effect on invasion in male mice while in females ~50% inhibition was observed, while moderate effect of licofelone (12% - 42% inhibition; p<0.005) and NO-Naproxen (38% - 42% inhibition; p<0.001) was observed. Importantly, the combination of two agents led to a synergistic effect leading to significant inhibition of both tumor growth (~80% in males; p<0.0001 and 55% females; p<0.0001) and invasion ~62% inhibition (p<0.0001) in both genders. Molecular analysis of urothelial tumors showed inhibitory effect on proliferation and inflammatory markers (PCNA, Cyclins, p53, p21, COX2, and IL1β). Our results suggest that safer dose combination of targeted agents may yield better chemopreventive effects than higher dose of individual agents. Specifically, NSAID plus CP may be a promising combination for preventing MIBC. (Supported in part by NCI-PREVENT program - NCI-CN-53300)

HIGH-DIMENSIONAL ANALYSIS OF TUMOR-INFILTRATING IMMUNE CELLS IN TREATMENT OF BREAST CANCER USING LASER IMMUNOTHERAPY

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Abstract

Metastatic breast cancer is one of the most challenging diseases to cure. Laser immunotherapy (LIT), using local administration of photothermal treatment (PTT) in combination with an immunoadjuvant, N-dihydrogalactochitosan (GC), has shown great promise in inhibiting tumor growth and suppressing metastases in both animal experiments and preclinical studies. However, the landscape of the immune cell compositions and transcriptome changes in response to LIT have not been fully understood. Here, we analyzed 49,380 individual immune cells collected from MMTV-PyMT mouse mammary tumors in four treatment groups (Control, PTT, GC and PTT+GC), using single cell RNA sequencing (scRNAseq). Our analysis revealed 18 major immune cell clusters. We also identified upregulated and downregulated genes in both myeloid and lymphoid cells as well as dynamic gene expression network induced by PTT, GC and PTT+GC treatment. We dissected the PTT+GC stimulated signaling pathways for each cell cluster and discovered ubiquitously upregulated pro-inflammatory cytokine pathways. We further studied the molecular signatures of T cells responding to PTT+GC. These results provided the cell atlas of breast tumor microenvironment and highlighted the important roles of pro-inflammatory pathways elicited by laser immunotherapy. Our high-dimensional analysis of tumor-infiltrating immune cells provided valuable insights for the mechanism of laser immunotherapy induced antitumor immunity.

TUMOR-TARGETED, PH-RESPONSIVE SILICA NANOPARTICLE AS A VEHICLE FOR IDENTIFICATION OF PANCREATIC CANCER VIA OPTOACOUSTIC IMAGING.

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Purpose: Inadequate early detection and inability to operate has led pancreatic ductal adenocarcinoma (PDAC) to be one of the most difficult types of cancer to treat. Non-specific symptoms coupled with quick metastasis result in a poor 5-year survival rate; ranging from 14% to as low as 1% depending on stage. Nanoparticles have recently emerged as a potential delivery agent for diagnostic and therapeutic agents, although clinical success has not been ample due to poor targeting. This shows a mesoporous silica nanoparticle functionalized with a PDAC-specific targeting ligand to exhibit specific particle release in malignant environment as compared to non-malignant environments.

Methods: Wormhole-pored mesoporous silica nanoparticles (MSNs) were formed using tetrapropyl orthosilicate (TPOS) and a hexadecyltrimethylammonium bromide (CTAB) scaffold. Following acid dialysis to remove CTAB and create worm-like pores, chitosan was added to coat the particles and serve as a gatekeeper. IR-780 was loaded into the particles with a series of acidification and basification procedures. Particle surfaces were functionalized to attach a PDAC-targeted, pH-low insertion peptide (V7). Pancreatic adenocarcinoma cells (S2VP10L) were plated in pH-7.4, 6.8, and 6.6 PBS solutions with V7-TPOS particles to assess uptake via near-infrared (NIR) fluorescence and multispectral optoacoustic tomography (MSOT). 8 hours following an IV injection of V7-TPOS, mice were imaged using MSOT to access targeting efficacy and biodistribution. Ex-vivo organ analysis was performed on the kidney, liver, spleen, and pancreas with NIR fluorescence.

Results: Zeta potential, DLS, and TEM were used to ensure proper size and characterization. NIR fluorescence imaging showed 15.8X while MSOT imaging showed 5X increased signal in malignant microenvironment. Ex-vivo data showed high amounts of probe were detected in the pancreas as compared to the liver, kidney, and spleen. Conclusion: The functionalized wormhole MSNs coated with chitosan demonstrated pH-sensitivity in terms of cellular uptake via NIR fluorescence and MSOT imaging.

EFFECTS OF E-CIGARETTE AEROSOL EXTRACTS ON CYTOCHROME P450 MONO-OXYGENASE ENZYMES

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Background and Aim: Electronic cigarettes (e-cigarettes) are devices that deliver an aerosol from a heated mixture of propylene glycol, vegetable glycerin, and flavors with or without nicotine. E-cigarettes have been reported to contain fewer harmful chemicals than tobacco smoke. However, the relative cancer risk associated with electronic cigarette use is still unknown. Despite unknown long-term health effects, the use of e-cigarettes has increased alarmingly over the past decade since they are marketed as a "safer" alternative to conventional tobacco. Currently, most e-cigarette users are either current smokers (dual users) or past smokers. Active smoking or exposure to tobacco smoke increases cancer risk. Cytochrome P450 (CYP) monooxygenases are intracellular enzymes that play a key role in the bio-activation of tobacco smoke procarcinogens such as benzo[a]pyrene into reactive metabolites that are carcinogenic. Here, we examined the effects of e-cigarette aerosol extracts exposure on the expression of CYP enzymes in oral epithelial cells.

Methods: E-cigarette aerosol extracts were collected from two brands of e-cigarettes, as previously described. Mainstream tobacco smoke (MS) extract was used as a positive control. Epithelial non-cancer, dysplastic, and cancer cell lines were exposed for 48 h to e-cigarette aerosol extracts at nicotine doses comparable to those observed in e-cigarette users. Whole-cell RNA and protein were isolated. Gene and protein expression were assessed by RNA-sequencing and western blotting. Data were analyzed by Student's t-tests and ANOVA models.

Results: Compared to vehicle control cells, exposure to e-cigarettes increased the mRNA and protein expression levels of key CYP enzymes involved in the metabolism of polycyclic aromatic hydrocarbons into carcinogenic intermediates. The levels of CYP enzymes in cells exposed to e-cigarette aerosol extracts were comparable to levels observed in tobacco smoke-exposed cells.

Conclusions: Overall, our study suggests that even short-term exposure to e-cigarette aerosol can induce CYP enzyme expression, thus allowing the cells to activate potentially harmful chemicals. These findings are particularly important in the context of dual e-cigarette and conventional tobacco users and pave the way towards understanding the role of e-cigarettes in cancer risk and cancer outcomes.

HISTO-MORPHOLOGIC CHARACTERISTICS OF THE POST BIOPSY SITE OF BREAST TUMORS

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Needle biopsy is essential for definitive diagnosis of breast lesion found by image screening. This procedure is known to result in a number of architectural changes in different types of tissues including breast tumor. However, no data has documented how biopsy-induced morphologic alterations are associated with clinical characteristics of the tumors, biopsy device, as well as patient demographic and medical history. The purpose of this study is to evaluate common histo-morphologic changes occurring in breast tumors following core needle biopsy.

We analyzed 50 breast tumor excisional specimens (Stage I-II) that had undergone prior core needle biopsy followed by surgery as the first definitive treatment. Whole-mount H&E stained sections from formalin fixed paraffin embedded blocks were reviewed by a breast pathologist. We found that the majority of breast tumor cases manifest a range of acute and chronic inflammation with the presence of neutrophils, eosinophils, lymphocytes, plasma cells, and histiocytes. Other findings include necrosis, giant cell reaction, granulation formation, residual biopsy marker induced material, and tumor growth in biopsy site. We are currently investigating to identify correlation between morphologic alterations and clinical characteristics breast tumor.

RACIAL SEGREGATION AND DISPARITIES IN TIMELY SURGERY IN BREAST CANCER PATIENTS

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Barriers to healthcare are a pervasive issue faced by racial minorities and individuals with low socioeconomic status. Studies have shown that black and Hispanic women with breast cancer are less likely than white women to receive timely and adequate treatment and experience greater mortality. Delay in surgery following cancer diagnosis is a common health disparity, and delay in surgery has been shown to be more frequent among blacks than white. While the roots of healthcare disparities are multifactorial, residential segregation, the physical separation of one racial/ethnic group from others, may account for the disparities in access to medical care. Since residential segregation is also more pronounced for blacks than any other racial/ethnic group in the U.S., segregation may be an important measure of racial/ethnic disparities in initiation of definitive treatment for breast cancer care.

The purpose of this study is to examine whether racial segregation is associated with disparities in timely breast cancer surgery or has a differential effect for different racial/ ethnic groups. This analysis is based on data from the Surveillance, Epidemiology, and End Results (SEER) Medicare database that is linked to Medicare claims on all incident cancer cases for persons over 65 years old with cancer residing in SEER program areas. Using a census tract-based isolation index, we will conduct multivariate analyses to understand the impact of racial segregation on the interval between breast cancer diagnosis and surgery.

THE ROLE OF NECROPTOSIS IN HEPATOCELLULAR CARCINOMA

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality in the world. The major risk factors for HCC development are chronic hepatitis B and C infections and chronic alcohol misuse. Recently, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) that are associated with obesity and metabolic syndrome are emerging as new risk factors for HCC development, especially in Western countries1. HCC is the best example of inflammation-linked cancer as more than 90% of HCC arise in the context of hepatic injury and inflammation. Necroptosis is a newly discovered non-apoptotic form of cell death that plays a major player in chronic inflammation2. However, the role of necroptosis-mediated inflammation in HCC is largely unexplored.

Mice deficient in the anti-oxidant enzyme Cu/Zn-superoxide dismutase knockout mice (Sod1-/- or Sod1KO mice) exhibit high oxidative stress in various tissues and >70% of old Sod1KO mice (18 to 22-month-old) develop spontaneous liver nodules that are reported to be either nodular hyperplasia or HCC3. We found that markers of necroptosis and inflammation are elevated in the liver of Sod1KO mice (9-month-old). Based on this, we hypothesized that necroptosis might play a role as the trigger for initiating inflammation in the liver of Sod1KO mice. To test our hypothesis, we inhibited necroptosis in Sod1KO mice either pharmacologically or genetically and assessed changes in inflammation. For pharmacological inhibition of necroptosis, Sod1KO mice were administered necrostatin1-s (Nec1-s, inhibitor of necroptosis pathway). Nec1-s treatment resulted in significant reduction in markers of necroptosis, transcript levels of pro-inflammatory cytokines (IL6, IL1⍺, and IL1β), and M1 macrophage markers in the liver Sod1KO mice liver, compared to Sod1KO mice treated with vehicle. Importantly, Nec-1s treatment also reduced liver weight and markers of fibrosis (Col1⍺1 and Col3⍺1) in the liver of Sod1KO mice. To assess the effect of genetic inhibition of necroptosis on inflammation, Sod1KO mice were crossed with Ripk3-/- mice (RIPK3 is a key molecule in the necroptosis pathway) to produce Sod1-/- mice that are heterozygous for Ripk3 (Sod1-/-Ripk3+/- mice). Sod1-/-Ripk3+/- mice also showed a significant reduction in the transcript levels of pro-inflammatory cytokines and triglyceride content in the liver. In summary, we show that necroptosis is activated in Sod1KO mice liver and blocking necroptosis reduces expression of pro-inflammatory cytokines in Sod1KO mice liver. These findings suggest that hepatic necroptosis might play an important role as the trigger for initiating inflammation associated with NAFLD in Sod1KO mice and necroptosis-mediated inflammation could be a potential target for the treatment of HCC.

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THE BIOLOGICAL IMPACT OF THE GOLGI MEMBRANE PROTEIN TMEM165 FOR BREAST CANCER

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The TMEM165 gene encodes for a multiple pass membrane protein, localized in the Golgi that has been linked to congenital disorders of glycosylation. We have identified TMEM165 as a biomarker for breast carcinoma in a previous glycoproteomic study. The TMEM165 protein is not expressed in non-malignant breast tissue, increases slightly in early stage ductal carcinoma in situ (DCIS) cases, and is highly expressed in invasive ductal breast cancer. Our hypothesis is that TMEM165 confers a growth advantage to breast cancer. In this preliminary study we created a CRISPR/Cas9 knockout of TMEM165 in the human invasive breast cancer cell line MDAMB231. Our results indicate that removal of TMEM165 in these cells results in a significant reduction of cell migration and tumor growth in vivo. These studies illustrate new potential functions for this Golgi membrane protein in the control of tumor cell growth and invasion.

CASE REPORT OF INTRAMUSCULAR DRY NEEDLING-ELECTRICAL STIMULATION FOR IMPAIRED HAND FUNCTION AFTER BRAIN TUMOR RESECTION

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Background/Purpose: Brain tumor resection can lead to movement dysfunction, often complicated by spasticity. Resulting activity/participation limitations warrant neuro-oncology rehabilitation, but spasticity narrows therapeutic options. Electrical stimulation (ES) is used to improve motor control following neurological insults, but surface electrodes may not achieve specific, dissociated contractions to retrain hand function. ES applied with Intramuscular dry needling (IMDN) is more localized, and may reduce tone, but there is limited evidence to guide IMDN-ES application for impaired upper extremity (UE) motor control with spasticity. In a case of benign brain tumor, improved spasticity (1 to 0 on modified Ashworth scale/MAS) and active wrist extension (from 40 to 53 deg) were reported after 3 sessions of DN without concurrent ES. Our purpose is to describe the application of IMDN-ES immediately prior to hand training, and sustained functional outcomes in an individual with disabling, chronic spasticity after brain tumor resection.

Case Description: A 31 year old male with right basal ganglia pilocytic astrocytoma, partially resected 2.5 yrs earlier, presented with left hemiplegia. UE spasticity, weakness, and decreased range of motion were greatest distally, and hand function had improved minimally with 2 years of intermittent rehab, including surface ES. He demonstrated 0 deg of active wrist extension, no dissociated finger movement, MAS grade 3 spasticity, was unable to repair his boat, and required an orthosis to fish. He estimated improvement in hand function after 2 yrs of therapy as 1+ (7+ = best) on the global rating of change (GROC) scale.

Intervention/Outcomes: IMDN (Needles .2x30mm)-ES was applied to left extensor carpi radialis longus, brevis, and ulnaris to elicit twitch response for 8 min before neuromuscular re-education. Immediate improvements included 23-deg increase in active wrist extension and spasticity reduction to 1+ with dissociated finger movement. These allowed participation in therapeutic interventions otherwise not feasible. Although <25% of spasticity and motion gains were retained to the next session, after 8 weekly sessions, he reported significant functional change (GROC 3+), and hand function to install a boat motor and fish independently without orthosis.

Discussion: This case highlights immediate but transient spasticity reduction with application of IMDN-ES. Dissociated finger movements allowed expanded in-clinic neurorehab. Spasticity reduction was transient, yet UE impairment, activity, and participation gains were sustained. While limitations of a single case report are many, this case is strengthened by repeated baseline. Formal research is needed using IMND-ES in individuals with spasticity and other hypertonicity resulting from brain tumors.

ALCOHOL EXCISE TAXES AS A PERCENTAGE OF PRICES IN OECD COUNTRIES

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Abstract:

Background: Excise taxes as a percentage of retail prices are considered as an indicator for tax burden and the effectiveness of sin taxes in reducing substance abuse. Despite the implementation of alcohol excise taxes in many countries, excise taxes as a percentage of alcohol prices have not been systematically studied.

Goal: In this study, we quantify excise taxes as a percentage of alcoholic beverage prices (beer, wine, and liquor) in Organization for Economic Cooperation and Development (OECD) countries, and evaluate the trends of taxes as a percentage of prices from 2003 to 2016.

Methods: The data on alcoholic beverage prices and excise taxes were gathered from the Economist Intelligence Unit (EIU) price city data and OECD tax database. The data were linked using year and country identifiers. The percentage of alcohol excise taxes in prices was calculated as the ratio of excise taxes to prices at three different price levels (maximum, mean, and minimum) for beer and wine, and at two different price levels (high end and low end) for liquors.

Results: Excise taxes as a percentage of average prices range from 4.3% in Luxemburg to 53.4% in Iceland for beer; and from 0.3% in France to 25.6% in Iceland for wine. With regards to excise taxes as a percentage of discount liquor prices, the range was from 5% in Czech Republic to 41.2% in Sweden for Cognac; from 15.7% in Canada to 67% in Sweden for Gin; from 12.6% in the US and Canada to 62.4% in Australia for Scotch Whisky six years old; and 9.7% in the US to 76.4% in Sweden for Liqueur Cointreau. The tax burden on liquor is higher than the tax burden on beer and wine, with wine bearing the least tax burden. Nonetheless, in most countries, the tax burden on beer and wine measured as a percentage of prices is lower than 30%. In most countries, taxes as a percentage of prices did not change significantly over time, with the only exception of Nordic countries where the percentage of taxes for wine and liquor increased and the percentage of taxes for beer decreased over time.

Conclusion: Compared to cigarettes, tax burden on alcoholic beverages is lower in OECD countries. In addition, in OECD countries other than Scandinavian countries, the percentage of taxes to prices did not change over time. There is sufficient room for increasing excise taxes, particularly for beer and wine.

FACTORS ASSOCIATED WITH PALLIATIVE CARE KNOWLEDGE AMONG AMERICAN ADULTS

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Background: Adequate knowledge of palliative care can help reduce disease burden and improve quality of life for cancer patients and their caregivers. Therefore, we examined factors associated with knowledge of palliative care among adults in the US. Our secondary objective was to identify the first and most trusted source for seeking information about palliative care. **Methods:** This retrospective, cross-sectional study utilized the 2018 National Cancer Institute's Health Information National Trends Survey (HINTS) 5, Cycle 2 to assess respondents' level of knowledge of palliative care. The primary outcome of interest was measured with the item "how would you describe your level of knowledge about palliative care?" Descriptive statistics were performed to determine the relationship between the outcome of interest and sociodemographic variables (e.g., race, age, gender). Multivariable logistic regressions, incorporating the sample weights, were conducted to identify the role of caregivers' status controlling for relevant sociodemographic variables. Jackknife replicate weights were used for population-level estimates. All analyses were conducted with survey commands using SAS 9.4 and significance level was set at $p < .05$. **Results:** Among the 3,504 respondents, more than 70% (n=2,283) had inadequate knowledge of palliative care. The majority of respondents were non-Hispanic white (n=1,961; 65.0%), ≥45 years old (n=2,542; 60.1%), female (n=2,011; 51%), married (n=1,726; n=52.6%), and had positive family history of cancer (n=2,429; 70.1%). Female gender (odds ratio [OR] =2.36, 95% confidence interval [CI] = 1.54–3.62), being married (vs. single; OR= 1.67, 95% CI = 1.03–2.71) and being employed (OR= 1.64, 95% CI = 1.15–2.34) were associated with increasing odds of adequate knowledge of palliative care. Those without a history of cancer (OR= 0.52, 95% CI = 0.33–0.83) and non-caregivers (OR= 0.54, 95% CI = 0.32–0.90) had lower odds of palliative care awareness. Also, compared to those aged 18-34 years, respondents aged 40-44 (OR= 2.24, 95% CI = 1.09-4.61) and 45+ (OR= 1.83, 95% CI = 1.08-3.10) reported greater odds of increased awareness of palliative care. Finally, compared with those with a high school education or less, those who have some college degree (OR= 5.58, 95% CI = 1.53-20.39) and college graduates or higher (OR= 11.63, 95% CI = 3.17-42.68) were more likely to be aware of palliative care. Healthcare providers were both the first (n=669; 59.3%) and the most trusted (n=920; 82.8%) source of information about palliative care. **Conclusions:** Variables predictive of knowledge of palliative care included education and employment status. These modifiable variables could be targeted for future interventions aimed at increasing overall knowledge of palliative care. Healthcare provide are the first and most-trusted source of information regarding palliative care and have a potential role in closing the gap in knowledge of palliative care in the US, given the low awareness of palliative care reported in our study.

SUBJECTIVE SOCIAL STATUS INDIRECTLY INFLUENCES SHORT-TERM SMOKING CESSATION THROUGH NICOTINE WITHDRAWAL SYMPTOMS

ABSTRACT

Few studies examine potential mechanisms linking subjective social status with smoking cessation. Thus, this study uses data from 146 adults enrolled in a smoking cessation program to evaluate whether subjective social status indirectly influences cessation through nicotine withdrawal symptoms. Findings indicated that subjective social status indirectly affected smoking cessation through withdrawal symptoms, specifically through anger and anxiety symptoms. People with a lower subjective social status report more withdrawal symptoms, particularly anger and anxiety, shortly after a quit attempt, and as such, are less likely to achieve smoking abstinence.

Keywords: subjective social status; smoking; tobacco; socioeconomic status; & withdrawal

USING GROWTH CURVE MODELLING TO ELUCIDATE THE ROLE OF AFFECT IN SMOKING CESSATION

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Background: It is well known that positive affect (PA) and negative affect (NA) are associated with smoking cessation. Yet, little is known about how changes in affective states may contribute to smoking abstinence.

Methods: This study used longitudinal data to examine the associations between PA and NA and smoking abstinence during a planned quit attempt. Data from a pilot three-armed randomized clinical trial of a smartphone-based smoking cessation intervention among adults (N=81) were used. Participants were asked to complete in-person computer-based surveys at four visits (baseline, quit date, 4 weeks post-quit and 12 weeks post-quit). The Positive and Negative Affect Schedule (PANAS) was used to assess PA and NA. Biochemically confirmed 7 day point prevalence smoking abstinence at 12 weeks post-quit was computed using self-report and a carbon monoxide monitor and was used as a moderator. Multilevel growth curve models were conducted to estimate the association between PA and NA and smoking abstinence controlling for age, sex, education, race (white vs. non-white), study group, and heaviness of smoking at baseline.

Results: Participants were primarily male (51.2%), white (67.9%), and 49.4 years old (SD=12.2). The abstinent rates were 17.3% at 12 weeks post-quit. Results indicated that participants whose PA increased throughout the trial were more likely to quit smoking while those whose PA decreased were less likely to quit smoking at 12 weeks post-quit (β=-2.78, p=.003). In contrast, participants whose NA decreased throughout the trial were more likely to quit smoking while those with increased NA were less likely to quit smoking (β=1.36, p=.02).

Conclusion: Decreasing PA and increasing NA may contribute to smoking relapse. Future smoking cessation interventions that detect and intervene to increase PA and decrease NA may increase cessation success.

DISCOVERY AND DEVELOPMENT OF DUAL MPGES-1 AND 5-LOX INHIBITOR LFA-9 AS A COLON CANCER CHEMOPREVENTIVE AND ANTI-INFLAMMATORY AGENT

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Chronic inflammation triggers tumorigenesis of the colorectum hence several non-steroidal anti-inflammatory drugs (NSAIDs) have been explored for prevention and treatment inflammatory diseases, including colorectal cancer (CRC). Traditional NSAIDs and COX-2 inhibitors though effective chemopreventive agents for CRC, however, unwanted side effects (gastrointestinal, renal and cardiovascular side effects) hinder their chronic use in high-risk cohorts. Mechanistic studies suggest that side-effects are in part COX-2 inhibition associated increase of 5-LOX metabolites and reduced PGI2 levels. Hence, target microsomal prostaglandin synthase-1 (mPGES-1) (spare PGI2) and 5-lipoxygenase may prove as effective and safer agents for chemoprevention. LFA-9 was designed based on pharmacophore of licofelone by adding 2-aminoethanoic acid (Glycine) at its carboxylic end for mPGES-1 and 5-LOX inhibition.

Here we characterized LFA-9 in detail, for its mPGES1/5-LOX selectivity over COX1/2 using in silico molecular modelling, in vitro enzyme activity assays, and ex vivo inhibition studies. Using human/mouse/rat mPGES-1 and 5-LOX enzymes to facilitate pre-clinical experimentation and clinical translation. In silico, LFA-9 showed strong binding affinity against 5-LOX (binding energies -199.85 & -215.3 Kcal/mol) and mPGES-1 (binding energies -238.27 & -257.76 Kcal/mol), but not with COX-1&2. LFA-9 substantially inhibited mPGES-1 (IC50 0.52 – 1.40 μM) and 5-LOX (IC50 0.89 - 2.75 μM) but not COX-1&2 (IC50>1mM) in cell free assays. Ex-vivo, LFA-9 inhibited PGE2 (IC50 0.47 – 0.78 μM) and LTB4 (IC50 0.66 - 1.24 μM) production and spared PGI2 (IC50>1 mM) and TXB2 (IC50>1 mM) production in LPS-stimulated human/mouse/rat macrophages and whole blood as the cell-based system. Circular dichroism and isothermal calorimetric based studies demonstrated that LFA-9 strongly binds and induces changes in secondary structure of human mPGES-1 and 5-LOX enzymes, thereby inhibits their activities.

Since PGE2 from mPGES1 activity promotes colon tumor stemness, LFA-9 was evaluated on colonic cancer organoids (spheroids) derived from PIRC (Polyposis in Rat Colon) rats that replicates human familial adenomatous polyposis. LFA-9 significantly inhibited colonic spheroids at 25 μM as compared to that of untreated control as well as licofelone. Anti-inflammatory properties of LFA-9 were evaluated in vivo studies using inflammogen (carrageenan)-induced rat paw edema model, dietary LFA-9 inhibited edema formation at after carrageenan injection. In summary, LFA-9 showed antiinflammatory and antitumor through mPGES1/5-LOX inhibition. Our data supports LFA-9, a novel mPGES-1 and 5-LOX inhibitor, as a safer drug candidate for prevention and therapy of colorectal cancer.

DNA DAMAGE DETECTION BY Q-PADDA: A PROMISING TOOL FOR ASSESSMENT OF CERVICAL CANCER RISK

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Background: Cervical cancer is the 4th most frequent cancer in women, accounts for ~200,000 deaths across the world. As per WHO, immunization against human papilloma virus (HPV), regular HPV screening, and the treatment of pre-cancerous cervical lesions could reduce death significantly. Cervical dysplasia, also referred as cervical intraepithelial neoplasia (CIN) is usually subdivided into low (CIN 1) and moderate/high grade (CIN 2/CIN 3). Moderate/high grade cervical dysplasia is considered a premalignant lesion. Chronic HPV infection increases DNA damage and reduces DNA repair, leading to even higher DNA damage levels. Recently, we showed that the levels of nuclear DNA (nDNA) damage are a potential biomarker to predictive head and neck cancer risk, which is associated with HPV infection. Herein, we performed a pilot study to assess whether the levels of nDNA damage can be used as a potential tool to screen cervical cancer risk.

Aims: (1) To measure the amount of nDNA damage in cervical samples with distinct pathologies. (2) To determine whether the number of nDNA lesions correlates with the grade of cervical dysplasia.

Methods: IRB was approved and consent was obtained from all participants. Cervix epithelial cells were collected using a cytobrush from 81 patients during their pelvic examination. Genomic DNA was extracted as previously reported. Demographic and risk factor data was collected through detailed questionnaires. Clinicopathologic data was abstracted from the medical chart. The amount of nDNA damage was quantified by q-PADDA, a highly sensitive primer-anchored DNA damage detection assay developed by our laboratory. Data were analyzed by Kruskal-Wallis test (non-parametric analysis) and logistic regression analysis was done to modeling the probability of having present pathology risk.

Results: Histopathological reports revealed that 27 cervical samples had no dysplasia (CIN0), 24 were CIN1 and 30 were CIN2/3. Our preliminary data (n=30) shows the amount of nDNA lesions per 10,000 bases increased by two-fold in CIN1 cases (p<0.05) and by about three fold in CINC2/3 cases (p≤0.02) when compared to no dysplasia (CIN0). Regression analysis showed no significant correlation between age, race, smoking and drinking status compare with pathology risk.

Conclusion: Our preliminary data shows that nDNA damage is the lowest in patients without cervical dysplasia and increases progressively with the grade of dysplasia and correspondent cancer risk. This pilot study shows the feasibility of the approach and stresses the potential of using nDNA damage to predict cervical cancer risk. Larger population studies are urgently needed to fully assess the potential of this approach for cervical cancer risk.

A COMPARISON OF DELAY DISCOUNTING BY E-CIGARETTE AND CIGARETTE USERS: IMPLICATIONS FOR U.S. FOOD AND DRUG ADMINISTRATION'S REGULATORY IMPACT ANALYSIS

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Background: Existing literature shows that delay discounting is associated with cigarette smoking. However, very limited evidence exists on the magnitude of delay discounting among exclusive e-cigarette users and among dual users of cigarettes and e-cigarettes. The association between delay discounting and choices of different tobacco products (i.e. e-cigarettes vs. cigarettes) is also unknown. Using the 2016 Georgia State University Tobacco Products and Risk Perceptions Survey of U.S. adults, this study compared the magnitude of delay discounting by tobacco use status, which are defined as nonuse, exclusive cigarette smoking, exclusive e-cigarette use, and dual use of cigarettes and e-cigarettes. The association between delay discounting and tobacco use outcome was also assessed.

Methods: Delay discounting was assessed using multiple price lists (MPL) with hypothetical monetary tradeoff payment between a smaller reward awarded today and a larger reward in the future (e.g. $19 today vs. $20 awarded 5 weeks from today). Wald test was used to compare the magnitude of delay discounting by tobacco use status and multinomial regressions were used to assess how delay discounting was associated with tobacco use status.

Results: 28% of nonusers, 29% of exclusive e-cigarette users, 31% exclusive cigarette smokers, and 34% dual users were hyperbolic discounters that have present biases. The prevalence of hyperbolic discounting did not differ by tobacco use status among the adult population. However, among younger adults aged 18-34, hyperbolic discounting is significantly higher among exclusive smokers than among nonusers and exclusive e-cigarette users. (p<0.05). Multinomial regression results further show that being a hyperbolic discounter is significantly associated with higher likelihood of being a smoker among young adults aged 18-34.

Conclusions: Hyperbolic discounting was significantly higher among young adult smokers aged 18-34. Being a hyperbolic discounter also was associated with cigarette smoking among young adults, suggesting that present bias may contribute to the decision to smoke cigarettes, but not to use e-cigarettes. Therefore, regulatory impact analysis should account for differences in lost consumer surplus by tobacco products.

STELLATE CELLS DERIVED HGF UNDER HYPOXIA RE-ACTIVATES PI3K/AKT PATHWAY AND CONTRIBUTES TO THE LIMITED SENSITIVITY OF EGFR INHIBITOR IN PANCREATIC CANCER

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Background: Oncogene-driven aberrant signalling in pancreatic cancer (PC) cells has been identified widely, but the signalling from stromal cells is poorly understood. Here, we showed the underlying mechanism of pancreatic stellate cells (PSCs) via secreting HGF suppress the sensitivity of EGFR inhibitor in PC under hypoxia

Experimental Design: The expression of PSCs marker and hypoxia marker in PC tissues were detected by immunohistochemistry, and their correlation with clinical characteristics were evaluated. Human immortalized PSCs were constructed and used to investigate its effect on PC cell lines by cell viability assay, cytokine chip, ELISA, RT-PCR, immunoblot, chromatin immunoprecipitation assay, and luciferase reporter experiment. An orthotopic xenograft mouse model was established to study effects of the combination of EGFR inhibitor with MET inhibitor in vivo.

Results: The simultaneously expression of markers of PSCs and hypoxia are associated with patient survival in PC, and the marker of PSCs positively correlated with the levels of hypoxia marker. HIF-1α regulates the expression of HGF in PSCs under hypoxia. PSCs-derived HGF acts on its receptor, MET, activates PI3K/AKT pathway in pancreatic cancer cells, which contributes to the suppression of EGFR inhibitor sensitivity.

Conclusions: Our study reveals a HIF-1α/HGF/MET/PI3K axis between PSCs and cancer cells in pancreatic cancer and suggests EGFR inhibitor in combination with MET inhibitor showed promising strategy in delaying pancreatic cancer development.

THE EFFECTS OF ELECTRONIC CIGARETTE FLAVORS ON WEIGHT GAIN AMONG CIGARETTE SMOKERS IN A SWITCHING TRIAL

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Background: Post-cessation (PC) weight gain is a barrier to smoking cessation. E-cigarettes (ECs) may aid smoking cessation efforts. Previous investigations of PC weight gain after switching to ECs showed gains of 2.4-2.9kg (12 & 24weeks-PC). No studies have evaluated weight gain by EC device, flavor, or nicotine concentration. Chemicals found in EC flavors are shown to disrupt glucose homeostasis and nicotine suppresses appetite, which in turn may affect weight. This study evaluated weight gain across two EC devices by flavor and nicotine concentration among cigarette smokers switching to an EC. **Methods:** Adult cigarette smokers (N= 233; 40.6±11.6 years; 64% female; 74% white) in a larger clinical trial evaluating the effects of low wattage (LW) vs. high wattage (HW) ECs vs. continued smoking on smoking behavior and biomarkers. EC flavor was categorized into four groups: tobacco, fruit, menthol, dessert. Participants selected nicotine concentration ranging from 3-24mg/ml. Weight gain was calculated as percent change in weight at each visit from baseline to 4, 12, 26, and 52 weeks. **Results:** The effect of EC liquid flavors and nicotine concentration on weight gain over time was not significant (p >.05); however, LW-EC users choosing the tobacco flavor exhibited weight gain during the study (gain at week 52 = 6.5%), while HW-EC tobacco flavor users lost weight (loss at week 52 = 3.4%). Fluctuations in weight were observed within other EC flavors by EC group. **Conclusions:** Differences in weight between LW and HW-ECs were observed, but no significant differences in weight gain by EC flavor or nicotine concentration. LW-EC tobacco flavor users exhibited the greatest risk for weight gain, while HW-EC users showed modest weight loss. Future studies examining the influence of flavor, nicotine, and device characteristics that may influence weight gain are needed.

GENETICALLY ENGINEERED TRAIL DELIVERY TARGETING DEATH-RECEPTORS FOR THERAPY RESISTANT PROGRESSIVE NEUROBLASTOMA.

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Neuroblastoma is the most common cancer in infants and accounts for 9.1% of childhood cancer-related deaths. Despite the current standard of care (SOC), drug-resistant neuroblastoma significantly compromises patient survival. Hence it is critical to identify new and less toxic therapeutic approaches for better patient outcomes. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which mediates its effect through the activation of the death receptor (DR) 4 and 5 are found on many cell types and are the main pathway for apoptosis. These can death receptors can kill most tumor cell types expressing TRAIL-receptor 1. Mining RNA-Seq data across multiple cohorts of neuroblastoma patients indicated that high levels of DR4 and DR5 significantly associated with poor clinical outcomes (OS, EFS, RFS). Further, examining the surface expression of DR4 and DR5 by immunohistochemistry using anti-human rabbit monoclonal antibodies on custom-archived TMAs for 100 NB patients revealed profound correlation with poor OS and RFS. Immunoblot analysis for DR4 and DR5 level in a panel of stage 4 patient-derived cell-lines during diagnosis and from progressive disease after therapy displayed high-levels of death receptor expression in progressive disease. Preliminary co-culture investigations with genetically engineered mesenchymal stem cells (MSCs) expressing tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) mimicking targeted delivery showed heightened differentiation and death (limited dilution tumorosphere assay) of therapy resistant cells. Further these studies exhibited inhibition of tumor cell migration and invasion. The results demonstrate the benefit of targeted TRAIL delivery in in the treatment of therapy resistant neuroblastoma and further imply that the genetically engineered MSCs could serve as a clinically valuable tool for improved therapeutic strategy in this setting.

OPPOSITE ROLES OF THE JMJD1A INTERACTION PARTNERS MDFI AND MDFIC IN COLORECTAL CANCER

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Abstract: MyoD family inhibitor (MDFI) and MDFI domain-containing (MDFIC) are homologous proteins known to regulate myogenic transcription factors. Hitherto, their role in cancer is unknown. We discovered that MDFI is up- and MDFIC downregulated in colorectal tumors. Mirroring these different expression patterns, MDFI stimulated and MDFIC inhibited growth of HCT116 colorectal cancer cells. Further, MDFI and MDFIC interacted with JMJD (Jumonji C domain-containing) 1A, a cancer-critical histone demethylase. JMJD1A influenced transcription of several genes that were also regulated by MDFI or MDFIC. Notably, the HIC1 tumor suppressor gene was stimulated by JMJD1A and MDFIC, but not MDFI, and HIC1 overexpression phenocopied the growth suppressive effects of MDFIC in HCT116 cells. Similar to colorectal cancer, MDFI was up- and MDFIC downregulated in breast, ovarian and prostate cancer, but both were overexpressed in brain, gastric and pancreatic tumors, indicating that MDFIC might inversely affect tumorigenesis in a tissue-specific manner. Altogether, our data suggest a tumor modulating function for MDFI and MDFIC in colorectal and other cancers that may involve their interaction with JMJD1A and a MDFIC-HIC1 axis.

MOBILITY-RELATED BASIC AND INSTRUMENTAL ACTIVITIES OF DAILY LIVING FLUCTUATE OVER 2-3 CYCLES OF CHEMOTHERAPY FOR OVARIAN CANCER IN WOMEN OVER 70: AN EXPLORATORY ANALYSIS.

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Objectives:

The purpose of this exploratory secondary analysis was to describe trajectories of Activities of Daily Living (ADLs) and Instrumental ADL (iADLs) ability in older (age >70) ovarian cancer (OC) patients over the course of chemotherapy (chemo), to inform selection of activities to query in prospectively monitoring for supportive care needs to improve chemo tolerance.

Methods:

This analysis of longitudinal data from an ongoing exercise feasibility pilot includes 17 women (Mean 75.90 SD ± 4.53 yrs) with Stage III-IV OC starting adjuvant (ADJ, n=5) or neoadjuvant (NEO, n=12) chemo. We included 3 iADL and 10 Physical Function Geriatric Assessment (GA) items, and 9 mobility-related ADLs/iADLs with 4-point ordinal scale: Independent, Modified, Assist, Unable. Surveys were collected before chemo Cycles 1, 2, 3 (and post-op for NEO). We used the Cumulative Link Mixed Model to test the time effect on 22 individual outcomes, and a likelihood ratio test to identify overall time effect, with significance level set at p=.05.

Results:

We identified significant time effects on 2 GA outcomes in NEO Group: Walk One Block (p=0.005) and Bathe/Dress (p=0.026), and 4 outcomes in ADJ Group: Walk Several Blocks (p=0.045), and 4-pt ordinal items of Toilet Transfers (p=0.044), Meal Prep (p=0.032), Shopping (p=0.005). Directional change (improve/worsen) differed by activity and group; While Walk One Block ability improved after C2 in NEO, Walk Several Blocks declined after C2 in ADJ. Bathe/Dress and Shopping declined after C1, but the decline partially reversed after C2.

Conclusions:

We identified 6 mobility-related ADL/iADLs of interest, differences by NEO/ADJ group, and unexpected trajectories of improvement or worsening across cycles. These results inform study design, and supportive care referrals for OC patients over age 70.

SUSCEPTIBILITY TO E-CIGARETTE USE AMONG YOUTH IN THE UNITED STATES: AN UPDATE FROM THE 2018 NATIONAL YOUTH TOBACCO SURVEY

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Significance: Multiple studies have evaluated youth susceptibility to e-cigarettes; however, few account for the changing landscape and introduction of new "pod-mod" e-cigarette, like JUUL. The goal of the present study was to build on previous investigations of youth susceptibility to use e-cigarettes, as well as provide an update of youth susceptibility factors using recent national data.

Methods: Secondary data analyses using the 2018 National Youth Tobacco Survey (NYTS) examined demographic (age, sex, race/ethnicity) and related factors (ever tobacco use, perceived ease of purchasing tobacco products, perceived harm, relative addictiveness, and household use of e-cigarettes/tobacco) associated with youth susceptibility to use e-cigarettes among never users (age = 12-17; n = 12,545). Weighted multivariable logistic regressions were used to model the odds of susceptibility to future e-cigarette use on sociodemographic factors, perceptions that it is easy to purchase tobacco products, perceptions of harm associated with e-cigarette use, relative addictiveness, ever tobacco use, and household use of tobacco products (OR; [95% CI]). Statistical analyses were weighted by primary sampling unit and sampling stratum to account for the complex sampling design using Stata/SE 15.1.

Results: Youth (never users) were more susceptible to use e-cigarettes if they were: younger (aOR = 1.1), female (aOR = 1.2), Hispanic (aOR = 1.3), perceived e-cigarettes as anything less than "extremely harmful" (aOR = 2.2-4.7), perceived tobacco products as "easy" to purchase (aOR = 1.4), had ever used tobacco (non e-cigarette products; aOR = 2.7), or reported household use of e-cigarette products (aOR = 1.5). Non-Hispanic black respondents (vs. non-Hispanic white: aOR: 0.77) had significantly reduced odds of susceptibility to e-cigarettes.

Conclusion: Given the rise in e-cigarette use among youth following the introduction of new pod-mod e-cigarettes, early education of associated harms of e-cigarettes on youth, particularly younger, female, and/or Hispanic youth, may reduce susceptibility and future initiation of e-cigarette use. Further, increasing in restrictions of e-cigarette sales (e.g., banning online sales) and increasing purchasing age to 21 may decrease perceptions of tobacco products and e-cigarettes as being "easy" to purchase. Longitudinal data following the emergence of e-cigarette experimentation is needed to assess additional patterns and predictors of e-cigarette use behaviors.

FEASIBILITY STUDY OF OPTICAL COHERENCE TOMOGRAPHY FOR PERCUTANEOUS NEPHROLITHOTOMY GUIDANCE

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Abstract: In percutaneous nephrolithotomy (PCNL), in order to remove the stones near the renal pelvis, nephroscope has to be inserted through a small incision in the patient's back. The scope has to penetrate the cortex and medulla in the kidney before reaching the stones near the renal pelvis. However, the current nephroscope only provide two-dimensional images and cannot distinguish different tissues in front of the scope tip. Furthermore, while the scope is penetrating the cortex and medulla, complications such as injury to the major blood vessels often occur, which possibly cause severe bleeding or even death afterwards. Optical coherence tomography (OCT) is a novel biomedical imaging technology for subsurface imaging of tissue samples with very high image resolution (~10 μm) and a penetration depth of several millimeters. In our study, we aim to evaluate the feasibility of OCT system for PCNL guidance. We imaged the different renal tissues at different depths in pig kidneys. Furthermore, glass capillary was buried into a pork kidney to mimic the blood vessels. The glass capillary was filled with intralipid solution and connected with the peristaltic pump. OCT can successfully distinguish different tissue types across different depths in the kidney. In addition, OCT can clearly visualize the glass capillary using Doppler effect. The study shows that OCT has great promise to guide nephroscope to the precise location and avoid damaging the blood vessels during insertion.

MECHANISMS LINKING PAIN AND SMOKING DURING A QUIT ATTEMPT

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ABSTRACT

Evidence suggests that pain is associated with smoking, but few studies have identified mechanisms that link pain with smoking. This study examined whether depressed mood, perceived stress, and smoking expectancies mediated the association between pain and smoking among adults enrolled in a three-armed clinical trial that compared in-person and smartphone-based smoking cessation interventions. Pain was measured at baseline. Perceived stress, smoking expectancies, and depressed mood were measured once daily, via a smartphone app, throughout the 1st week of the quit attempt; these variables were aggregated for analyses. Biochemically confirmed (CO <7 ppm) 7-day point-prevalence smoking abstinence was measured 4 weeks post-quit date. Participants (N=81) were mostly White (63%) and on average, 49 years of age. At baseline, participants reported moderate nicotine dependence on the Heaviness of Smoking Index (M=1.2, SD=0.5), and 54% of participants reported experiencing moderate or severe pain. Sequential mediation analyses showed that participants who reported moderate or severe pain, compared to none or mild pain, felt more stressed (B=0.54, SE=0.19, p=0.01) and depressed (B=0.76, SE=0.20, p<0.01). Higher stress (B=0.42, SE=0.12, p <0.01) and depression (B=0.26, SE=0.12, p=0.03) were associated with greater belief that smoking would improve mood (e.g., smoking expectancy), which was, in turn, associated with higher odds of smoking four weeks after the quit attempt (OR=2.49 [95% CI=1.13, 5.50]). Path analyses indicated that pain indirectly increased the odds of smoking through the stress/smoking expectancy pathway by 20% (OR=1.20 [95% CI=1.00, 2.27]) and the depression/smoking expectancy pathway by 20% (OR = 1.20 [95% CI=1.00, 1.85]). Findings suggest that pain may induce stress and depression, and people who feel depressed or stressed may believe that smoking would improve their mood, which subsequently may increase their risk of smoking lapse. Interventions that treat people with moderate or severe pain may need to provide psychoeducation that teaches adaptive coping responses, such as physical activity, for stress and depression.

TREATMENT OF BREAST CANCER TUMORS AND LEUKEMIA WITH NOVEL ANNEXIN A5 - DRUG CONJUGATES

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Introduction: The untargeted systemic chemotherapy commonly used to treat many cancers has many negative effects on healthy organs and tissue. Here we report, two novel protein-drug conjugates have been created and are targeted to cancer cells.

The novel conjugates we developed consist of the protein annexin A5 (ANXA5) linked to either chlorambucil (CMB) or mertansine (DM1). ANXA5 binds specifically to the phospholipid phosphatidylserine (PS) on the outer membrane of cancer cells. PS is not expressed on healthy cells, so the conjugates will not bind. CMB, an aromatic nitrogen mustard derivative, is an alkylating agent that interferes with DNA replication and induces cellular apoptosis via the accumulation of cytosolic p53 and subsequent activation of Bax, an apoptosis promoter. DM1 is a tubulin inhibitor that inhibits the assembly of microtubules by binding to tubulin, leading to mitotic arrest and apoptosis.

Materials and Methods: Recombinant ANXA5 (molecular mass 36 kDa) was expressed in E. coli and purified to homogeneity. CMB was linked to ANXA5 using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-hydroxysulfosuccinimide (sulfo-NHS), and DM1 was linked to ANXA5 using sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC). Typical loadings of 10-12 CMB molecules per ANXA5 and 6-9 DM1 molecules per AXNA5 were observed. For the study in mice, Balb/c female mice (n = 6), 6 weeks of age, were inoculated with an orthotopic injection of 105 4T1 cells in the mammary fat pad on day 0. The mice received 0.5 to 5.0 mg CMB/kg mouse weight daily of the ANXA5-CMB conjugate.

Results and Discussion: The two conjugates have been tested in vitro for their effectiveness against two mouse breast cancer cell lines and two mouse leukemia cell lines. Compared to the free drugs for 4T1 and EMT6 breast cancer cells, the conjugates were 42 to 377 times more effective when comparing the IC50 (concentration where the viability is reduced by 50%) values obtained. For P388 and L1210 leukemia cells, the conjugates were 16 to 354 times more effective compared to the free drugs. The ANXA5-CMB conjugate was tested for treating mice with syngeneic orthotopic 4T1 breast tumors at a dose of CMB in the conjugate of 0.5 mg / kg mouse weight. At this dose administered daily, the tumors were significantly smaller (approximately 5 times) compared to treating at this same dose of free drug after 9 days of treatment. Research is continuing to optimize the dosage.

Conclusions: Remarkable increases in the effectiveness of the two anticancer drugs have been obtained by the linkage of the drugs to ANXA5. This targeted approach to treating cancer has the potential for an effective treatment of cancer with a large reduction in side effects.   Future work will focus on optimizing the dosage of the conjugate in tests in mice using several breast cancer and leukemia cell lines.

CANCER STEM CELL MARKER DCLK1 CORRELATES WITH TUMORIGENIC IMMUNE INFILTRATES IN THE COLON AND GASTRIC ADENOCARCINOMA MICROENVIRONMENTS

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Abstract: Immunotherapy that has proved efficacy in several solid cancers plays a partial role in improving clinical outcomes of advanced gastrointestinal (GI) cancers. There is an unmet need to find new immune-related therapeutic targets. Doublecortin-like kinase 1 (DCLK1) marks tuft cells which are recognized as cancer initiating cells and regulators of the type II immune response, and has been studied for its role in many cancers including colon and gastric cancers, but its role in tumor immunity remains unexplored. In the current study, we analyzed colon and gastric cancer RNA sequencing data from 283 and 415 patients respectively from The Cancer Genome Atlas (TCGA). High DCLK1 expression predicted the worse clinical outcomes in colon and gastric cancer patients and correlated with increased immune and stromal components. Further analysis indicated that DCLK1was strongly linked to infiltration of multiple immune cell types, especially TAMs and Tregs, and strongly correlated with increased CD8+ T cell inhibitors TGFB1 and CXCL12 and their receptors, suggesting it may contribute to TAM-mediated inhibition of CD8+ T cells. Interestingly, we found that DCLK1 was a prognostic biomarker in left-sided colon cancer which has worse outcomes and demonstrates a reduced response to existing immunotherapies. In conclusion, our results demonstrate that DCLK1 is linked with functional regulation of the tumor microenvironment and may have potential as a prognostic biomarker and adjuvant target to promote immunotherapy sensitivity in colon and gastric cancer patients.

IDENTIFICATION OF IMMUNE SUBSETS MARKERS, CCL22, ZNF366, AND GPR114, AS CANDIDATE REGULATORS OF GENOMIC INSTABILITY IN HUMAN LUNG ADENOCARCINOMA

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(a) Chromosome instability (CIN), a type of genomic instability that is mitotic error-driven, has a deep impact on carcinogenesis and cancer recurrence. High CIN is a marker for poor prognosis in various cancers, including lung adenocarcinoma. In the tumor genome, CIN can be indicated with Copy Number Alterations (CNA) as its surrogate indicator. Although a diverse array of genes can cause CIN at the cellular level, genes responsible for tumor CNA remain elusive. In this study, we set out to identify genes whose expression shows correlation with CNA in human lung adenocarcinoma.

(b) We employed a novel cross-species in silico analysis. Our previous lung RNAseq results from lung cancer-prone CIN mice indicated 348 misregulated genes (92 up-regulated, 256 down-regulated; 2-fold cutoff, $P<0.05$). We hypothesized that some of the genes misregulated in CIN mice are involved in genomic instability in tumors. With in silico analysis with a human cancer genome database, we identified five human genes as candidate regulators of CNA in human lung adenocarcinoma: MMP13, NUF2, CCL22, ZNF366, and GPR114. High expression of MMP13, CCL22, ZNF366, and GPR114 was correlated with low CNA, suggesting their role in suppressing CIN. High expression of NUF2 was correlated with high CNA, suggesting its role in increasing CIN.

(c) MMP13 (Matrix Metalloprotease 13) is a protease involved in the breakdown of extracellular matrix. NUF2 (yeast NUF2 Kinetochore Protein homolog) is involved in the mitotic process, the misregulation of which directly leads to CIN. CCL22 (C-C Motif Chemokine Ligand 22), ZNF366 (Zinc Finger Protein 366), and GPR114 (G protein-coupled receptor 114, aka ADGRG5) are generally markers for subsets of immune cells (likely dendritic cells). This result led us to further hypothesize that infiltration of CCL22-, ZNF336-, and/or GPR114-positive immune cells inhibits pre-tumor cells and tumor cells with high CNA.

(d) The removal mechanism of cells with genomic instability is poorly understood. This is the first time that candidate markers for the immune cells directly or indirectly involved in removal of CIN cells have been identified. This study may aid in fine-tuning cancer-preventive immunotherapy that targets lung cells with genomic instability.

DEPTH-RESOLVED IMAGING OF BLADDER TUMOR USING OPTICAL COHERENCE TOMOGRAPHY AND FLUORESCENCE LAMINAR OPTICAL TOMOGRAPHY

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Abstract: Early detection of neoplastic changes remains a critical challenge in clinical cancer diagnosis and treatment. Many cancers arise from epithelial layers such as those of the urinary bladder. Current standard endoscopic technology is unable to detect those subsurface lesions. Since cancer development is associated with both morphological and molecular alterations, imaging technologies that can quantitative image tissue's morphological and molecular biomarkers and assess the depth extent of a lesion in real time, without the need for tissue excision, would be a major advance in bladder cancer diagnostics and therapy. In this research, we investigated the feasibility of multi-modal optical imaging including high-resolution optical coherence tomography (OCT) and depth-resolved high-sensitivity fluorescence laminar optical tomography (FLOT) for structural and molecular imaging. UPII-SV40T mice bladder tumor models were imaged using OCT and FLOT and the correlated histopathological diagnosis was obtained. Quantitative structural (the scattering coefficient) and molecular imaging parameters (fluorescence intensity) from OCT and FLOT images were developed for multi-parametric analysis. This multi-modal imaging method has demonstrated the feasibility for more accurate diagnosis. This project results in a new non-invasive multi-modal imaging platform for improved bladder cancer detection, which is expected to have a major impact on detection, diagnosis, and characterization of bladder cancers, as well as a wide range of epithelial cancers.

ACSS2 PROMOTES PANCREATIC CANCER CELLS SURVIVE NUTRIENT DEFICIENCY BY UPREGULATING ZIP4

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Background: The microenvironment of pancreatic ductal adenocarcinoma (PDAC) is characterized with desmoplasia and nutrient deficiency. ACSS2 has been shown to help tumor cells survive in energy stress environment. Zinc transporter, ZIP4 plays an important role in inducing cachexia, metastasis and chemoresistance in PDAC. In this study, we aim to investigate whether and how ACSS2 and ZIP4 can help PDAC cells survive in nutrition limited microenvironment.

Methods: Nutrition limited microenvironment was established by reducing the concentration of serum in cell culture medium. The correlation of ACSS2 and ZIP4 expression in human PDAC tissue was analyzed by qPCR and TCGA database. The ACSS2 knocked-out cell lines were established with CRISPR/Cas9 system followed by the selection of mono-colony. The proliferation rates of ACSS2 knocked-out PDAC cell lines were measured by MTT assay. Correlations between ACSS2 and downstream pathway p-Akt/p-GSK-3β were studied with Western blot.

Results: Nutrition limited microenvironment can induce the upregulation of ZIP4 expression in PDAC cells in an ACSS2 dependent manner. TCGA RNA-seq data analysis showed that the expression of ACSS2 in human PDAC tissue was positively correlated to the expression of ZIP4. The proliferation rates of two PDAC cell lines, AsPC-1 and CFPAC-1, were significantly decreased when we knocked out ACSS2. Knock out ACSS2 can decrease the expression of ZIP4 in an AKT/GSK-3β pathway dependent manner. Metformin can decrease the expression of ZIP4, partially by inhibiting the AKT/GSK-3β pathway.

Conclusion: ACSS2 can upregulate ZIP4 expression by activating AKT/GSK-3β pathway in nutrition deficient PDAC microenvironment, which may serve as a potential therapeutic target for PDAC treatment.

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CHALLENGING CLINICAL NUTRITION ASSUMPTIONS: HIGHER BODY WEIGHT PREDICTS LOWER PRE-OP PROTEIN INTAKE BEFORE PANCREATICODUODENECTOMY

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Background: Pancreatic head cancer has a one-year relative survival rate of 20%. Surgical resection is the only chance at cure, but 40-70% of patients who undergo pancreaticoduodenectomy (PD, or 'Whipple') have peri-operative complications that impact quality of life, and can prevent the adjuvant chemotherapy needed for optimal survival outcomes. Evidence suggests dietary protein intake is important for surgical recovery, and most patients do not meet national recommendations of 1.2 grams of protein/kg body weight pre-operatively. Even so, assessment by a nutrition professional is not standard of care, and there are no guidelines for other healthcare professionals who must decide which patients to refer to a dietitian. Referrals may be based on low body weight, assumed to directly reflect lower protein intake.

Purpose: We aim to determine whether body weight and total daily calorie intake can predict pre-op daily protein intake in patients awaiting PD for pancreatic and related cancers and pre-cancers.

Methods: This is a cross-sectional exploratory analysis of baseline data collected 2-weeks before PD, in an ongoing pilot RCT of exercise and nutrition prehabilitation. Daily intake of dietary protein (DPI) and total calories (DCI) was estimated from a dietitian-administered 24-hour Food Recall survey. Body Weight (BW) was measured by Bioelectrical Impedance. We performed statistical analysis using a multivariate linear regression model with alpha 0.05.

Results: 62 patients (46.8% female, age 66.7 ± 11.5 yrs., 90.3% non-Hispanic white) had complete data for inclusion in this analysis. All prospectively consented between 2016 and 2019. Mean DPI was 0.85 ± 0.39 g/kg, and only 12 people (19.4%) met 1.2 g/kg threshold. Mean DCI was 1623.7 ± 610.6 kcal, and BW was 178.9 ± 38.5 lbs in this cohort of mean height 67.1 ± 11.5 in. In multivariate regression, BW (beta = -0.122) and DCI (beta = 0.300) significantly predicted DPI (p<0.001).   The observed dependent variables moderately correlated (R=0.837) with values predicted by the final model.

Conclusions: Few patients at Stephenson Cancer Center meet national dietary protein recommendations at time of consent for PD, and while lower protein intake associated with lower total calorie intake, it also associated with higher body weight. This latter finding challenges a clinical assumption that could prevent survivors with lowest protein intake from being referred for nutritional intervention. These findings support the need for further research on interventions to improve pre-operative dietary protein intake, and the specific, independent role of dietary protein in PD outcomes.