NCI Cancer Center

2023 Annual Cancer Research Symposium

Friday, March 10, 2023

OU Health | Stephenson Cancer Center

The Stephenson Cancer Center wishes to recognize and thank the Oklahoma Tobacco Settlement Endowment Trust (TSET) for co-sponsoring the 2023 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 and in 2022 for an additional three 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.

Ten Year Highlights

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

- Increased cancer center membership from 56 to 289 members at nine academic institutions across Oklahoma
- Recruited seventy one 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 330 research seminar speakers
- Hosted annual statewide Cancer Research Symposium that bring together over 250 researchers from around the state
- Hosted over 90 undergraduate students from 32 different universities for summer cancer research experience.
- Since the inception of the TSET grant, the SCC has enrolled more than 7,000 patients to interventional clinical trials.

Health Promotion Research Center

OU Health Stephenson Cancer Center wishes to recognize and thank the TSET Health Promotion Research Center (HPRC) for co-sponsoring the 2023 Annual Cancer Research Symposium

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The TSET Health Promotion Research Center (HPRC) is a leading research program with a focus on the entire translational continuum – from the discovery of basic mechanisms of health behavior and behavior change, to the development and evaluation of novel interventions, to the dissemination and implementation of interventions, policies, and education throughout Oklahoma.

The **mission** of the HPRC is to reduce the burden of disease in Oklahoma by addressing modifiable health risk factors such as tobacco use, sedentary lifestyle, poor diet, and risky alcohol and other substance use through research, novel intervention development, and dissemination of research findings.

The HPRC contains four major resources that facilitate research: Mobile Health Shared Resource, Tobacco Treatment Research Program, Postdoctoral Fellowship Training Program, and Tobacco Regulatory Science Clinical Laboratory.

The center was established in 2007 with funding from the Oklahoma Tobacco Settlement Endowment Trust (TSET) as part of their efforts to support statewide and community-based cessation and intervention projects.

HPRC Directors, Faculty
Michael Businelle, PhD (Director)
Darla Kendzor, PhD (Director)
Adam Alexander, PhD
Desiree Azizoddin, PsyD
Than Bui, MD, DrPh
Meng Chen, PhD
Amy Cohn, PhD
Lance Ford, PhD
Summer Frank-Pearce, PhD
Amanda Kong, PhD
Julia McQuoid, PhD
Jordan Neil, Ph.D.
Motolani Ogunsanya, PhD
Jason Oliver, PhD
Lurdes Queimado, MD, PhD
Katelynn Romm, PhD
Erin Vogel, PhD

TSET

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2023 Annual Cancer Research Symposium

9:00 – 9:30 am	**Registration & Poster Check-In** Nicholson Tower Auditorium Lobby – Floor 5
9:30 – 9:45 am	**Welcome & State of the Cancer Center** Nicholson Tower Auditorium
9:45 – 9:50 am	**DEI Panel Introduction** Nicholson Tower Auditorium
9:50 – 10:35 am	**DEI Panel Discussion** Nicholson Tower Auditorium
10:35 – 11:40 am	**ACS-IRG Awardee Session** Nicholson Tower Auditorium
11:40 – 1:15 pm	**Lunch and Poster Session** Nicholson Tower Auditorium Lobby Nicholson Tower Rooms C, D, E, & F – Floor 5
1:15 – 2:20 pm	**Session I – Joint Program Session** Nicholson Tower Auditorium
2:20 – 2:30 pm	**Break**
2:30 – 3:35 pm	**Session II – Programmatic Assignments** Cancer Biology – Nicholson Tower Auditorium Cancer Prevention & Control – Nicholson Room A Cancer Therapeutics – Nicholson Room B
3:40 – 4:45 pm	**Session III – Programmatic Assignment** Cancer Biology – Nicholson Tower Auditorium Cancer Prevention & Control – Nicholson Room A Cancer Therapeutics – Nicholson Room B
4:40 – 4:55 pm	**Break**

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4:55 – 5:10 pm	**Awards/Closing Remarks** Nicholson Tower Auditorium
5:10 – 6:15 pm	**Reception** Nicholson Tower Lobby

2023 Annual Cancer Research Symposium

9:00 – 9:30 am
Registration & Poster Check-In
Nicholson Tower Auditorium Lobby – Floor 5

9:30 – 9:45 am
Welcome & State of the Cancer Center
Nicholson Tower Auditorium
Robert S. Mannel, MD

9:45 – 9:50 am
DEI Panel Introduction
Nicholson Tower Auditorium
Robert S. Mannel, MD

9:50 – 10:35 am
DEI Panel Discussion
Nicholson Tower Auditorium
LaKaija Johnson, PhD
Lancer Stephens, PhD
David Conkerite II, MBA, SPHR
Adam Alexander, PhD
Robert Salinas, MD, CAQ(G)
Joan Walker, MD
Moderator: Amanda Kong, PhD, MPH

10:35 – 11:40 am
ACS-IRG Awardee Session
Nicholson Tower Auditorium
Moderator: Stefano Tarantini & Stevie Warner

THE FEASIBILITY OF OFFERING ESCALATING INCENTIVES TO PROMOTE SMOKING CESSATION AMONG ADULTS WITH TYPE 2 DIABETES
Sydney Martinez

DISPARITIES IN OUTCOMES AMONG CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN OKLAHOMA, 2005-2019
Amanda Janitz

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2023 Annual Cancer Research Symposium

"IT FREES YOUR BODY FROM THAT PAIN THOUGHT": UNDERSTANDING CANNABIS USE FOR PAIN AMONG OLDER RESIDENTS OF RURAL COMMUNITIES
Julia McQuoid

11:40 – 1:15 pm **Lunch & Poster Session**
Nicholson Tower Auditorium Lobby
Nicholson Tower Floor 5, Rooms C, D, E, & F

1:15 – 2:20 pm **Session I – Joint Program Session**
Nicholson Tower Auditorium
Moderators: Resham Bhattacharya & Min Li

RPRD1B IS A DNA REPAIR PROTEIN THAT SUPPRESSES TUMOR FORMATION AFTER GENOTOXIC STRESS
Julio Morales

EMPLOYING COMMUNITY-BASED AND MHEALTH INTERVENTIONS TO REDUCE PROSTATE CANCER DISPARITIES AMONG AFRICAN AMERICANS: A MULTILEVEL APPROACH
Ruosi Shao

IMMUNOGENIC TREATMENT FOR METASTATIC BREAST CANCER USING TARGETED CARBON NANOTUBE-MEDIATED PHOTOTHERMAL THERAPY IN COMBINATION WITH CHECKPOINT INHIBITION AND IMMUNOADJUVANT
Gabriela Faria

2:20 – 2:30 pm **Break**

2023 Annual Cancer Research Symposium

2:30 – 3:35 pm **Session II**

Cancer Biology Track

Nicholson Tower Auditorium
Moderator: Deepa Sathyaseelan & Elizabeth Wellberg

NNT-AS1 MEDIATED REGULATION OF NNT IN OVARIAN CANCER
Shailendra Dwivedi

CIRCULAR RNA ANAPC7 INHIBITS TUMOR GROWTH AND AMELIORATES MUSCLE WASTING VIA PHLPP2–AKT–TGF-B SIGNALING AXIS IN PANCREATIC CANCER
Jingxuan Yang

TUMOR TARGETED IMMUNO-LIPOSOMAL RD3 DELIVERY DIVERTS MIR PROGRAMING IN RD3 NULL AGGRESSIVE AND PROGRESSIVE NEUROBLASTOMA CELLS
Sreenidhi Mohanvelu

Cancer Prevention & Control Track
Tobacco Use and Cessation

Nicholson Tower – Room A
Moderator: Darla Kendzor

EFFECTS OF A NICOTINE WARNING LABEL AND VAPING CESSATION RESOURCES ON YOUNG ADULTS PERCEPTIONS OF PRO-VAPING INSTAGRAM INFLUENCER POSTS
Erin Vogel

DISPARITIES IN JOINT TRAJECTORIES OF CIGARETTE AND E-CIGARETTE USE ACROSS SEXUAL ORIENTATION GROUPS OF YOUNG ADULT MEN AND WOMEN IN THE US
Katelyn Romm

GENDER-SPECIFIC MOTIVES AND BARRIERS FOR TOBACCO SMOKING CESSATION IN LAO PEOPLES DEMOCRATIC REPUBLIC
Shweta Kukarni

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E-CIGARETTE AEROSOLS INDUCE THE EXPRESSION OF NRF2 AND ITS DOWNSTREAM TARGETS IN HUMAN BRONCHIAL CELLS AND MODULATE INFLAMMATORY MARKERS
Vengatesh Ganapathy

Cancer Therapeutics Track

Nicholson Tower – Room B
Moderator: Laura Holman

ASSOCIATION BETWEEN NEEDLE DENSITY AND TREATMENT OUTCOMES IN PROSTATE CRYOTHERAPY
Danielle Digoy

TARGETING SOLVENT-FRONT MUTANTS OF THE RET ONCOKINASE
Ujjwol Khatri

3:40 – 4:45 pm **Session III**

Cancer Biology Track

Nicholson Tower Auditorium
Moderators: Ralf Janknecht & Jerry Wu

EXOSOMAL UCA1 REPROGRAMS GLUCOSE METABOLISM IN PERITUMORAL FIBROBLASTS IN OVARIAN CANCERS
Revathy Nadhan

PROTEOMIC STUDIES OF INTERACTIONS BETWEEN DRUG-RESISTANT AND DRUG-SENSITIVE CANCER CELLS
Zongkai Peng

THE ROLE OF NECROPTOSIS ASSOCIATED CHRONIC INFLAMMATION IN THE DEVELOPMENT OF LIVER CANCER
Ramasamy Selvarani

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Cancer Prevention & Control Track
Cancer Survivorship

Nicholson Tower – Room A
Moderator: Paul Spicer

EXPLORING BIOIMPEDANCE PHASE ANGLE TRAJECTORIES AFTER HIGH-FREQUENCY PREHABILITATION FOR PANCREATICODUODENECTOMY
Abby Cha

PERIPHERAL NEUROPATHY PHENOTYPING IN GYNECOLOGIC CANCERS SUGGESTS MOTOR PREDOMINANCE
Elizabeth Hile

LONGITUDINAL APPLICATION OF DATA-DRIVEN MODELLING TO ANALYZE HEEL-TOE PLANTAR PRESSURE TRAJECTORIES IN WOMEN WITH GYNECOLOGIC CANCER DURING NEUROTOXIC CHEMOTHERAPY
Hazem Refai (Ahmed Elsebaay)

ARTIFICIAL INTELLIGENT FRAMEWORK USING PLANTAR PRESSURES TO DISTINGUISH CLINICAL PERIPHERAL NEUROPATHY PHENOTYPES IN WOMEN'S CANCERS
Kangjun Seo

Cancer Therapeutics Track

Nicholson Tower – Room B
Moderator: Susanna Ulahannan

SINGLE-CELL RNA SEQUENCING REVEALS ANTI-TUMOR PHENOTYPES IN NK CELLS INDUCED BY BOTH LOCALIZED ABLATIVE IMMUNOTHERAPY (LAIT) AND IMMUNE CHECKPOINT INHIBITOR (ICI) THERAPY
Kaili Lu

ULTRASOUND IMAGING OF PD-L1 IMMUNE MARKERS BY TARGETED MICROBUBBLES IN A MURINE COLON CARCINOMA MODEL
Negar Sedeghipour

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TREATMENT-RELATED COGNITIVE IMPAIRMENT IN CANCER PATIENTS
Summer Edwards

4:40 – 4:55 pm	**Break**
4:55 – 5:10 pm	**Awards/Closing Remarks** Nicholson Auditorium
5:10 – 6:15 pm	**Reception** Nicholson Lobby

DEI PANEL DISCUSSION

DEI PANEL DISCUSSION

Nicholson Tower – Auditorium

9:50 – 10:35 AM

DEI PANEL DISCUSSION

Moderator: Amanda Kong, PhD, MPH

Panelists:
LaKaija Johnson, PhD
Assistant Vice President for Diversity, Equity, and Inclusion for Regional Connections

Lancer Stephens, PhD
Associate Professor of Research
Associate Dean for Sovereignty, Equity, Diversity, & Inclusion

David Conkerite II, MBA, SPHR
Associate Vice President - Diversity, Equity, and Inclusion

Adam Alexander, PhD
Assistant Professor
Assistant Director for Diversity, Equity, and Inclusion

Robert Salinas, MD, CAQ(G)
Associate Professor
Assistant Dean, OUCOM, Office of Diversity, Inclusion, and Community Engagement

Joan Walker, MD
Professor
Associate Director of Diversity, Equity and Inclusion

THINKING BIG: IMPLEMENTING A STRATEGIC PLAN TO ENHANCE DIVERSITY, EQUITY, AND INCLUSION AT THE STEPHENSON CANCER CENTER

Amanda Kong (Moderator),[a,b] LaKaija Johnson(Panelist),[c] Robert Salinas (Panelist),[b] Lancer Stephens (Panelist),[d] Joan Walker (Panelist),& Adam Alexander (Organizer)[a,b,e]

[a] Health Promotion Research Center, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

[b] Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

[c] Office of Diversity, Equity, and Inclusion, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

[d] Department of Health Promotion Sciences, Hudson College of Public Health, University of Oklahoma Health Sciences Center

[e] Department of Obstetrics and Gynecology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

The National Cancer Institute (NCI) requires that all cancer centers affiliated with the NCI Cancer Centers Program develop strategies to recruit and retain cancer center membership and leadership that reflects the nation's diversity. Presently, women represent 36% of faculty members within NCI-designated cancer centers, and racial and ethnic minorities (e.g., African Americans, Hispanics, and American Indians) represent less than 6% of the faculty population. Women and minorities are even less represented in cancer center leadership positions. Increasing diversity within cancer centers will be paramount for eliminating health disparities, improving patient outcomes, and reducing healthcare costs, especially as racial and ethnic minorities become a greater percentage of the US population.

The Stephenson Cancer Center (SCC) leads the nation in diversifying its membership and leadership. At SCC, women represent almost 42% of all faculty members, and minorities represent 11%. Further, more than 30% of all research leadership positions are held by women, and minority faculty members hold 13% of these positions. With the establishment of the Office of Diversity. Equity and Inclusion (O-DEI) at SCC, there is an opportunity to build on the cancer center's success by implementing new and innovative strategies to further enhance current efforts to diversify cancer center membership and leadership. O-DEI has invited several institutional leaders and representatives to participate in a panel discussion to outline their ongoing strategies and challenges to diversify faculty and leadership on OU and OUHSC campuses. Through conversations with panel members and feedback and interaction with the audience, the

primary goal of this panel discussion is for O-DEI and SCC to refine planned strategies and discover new approaches that can be implemented as a team and organization to further enhance diversity, equity, and inclusion at the Stephenson Cancer Center.

ACS-IRG AWARDEE SESSION

ACS-IRG Awardee Session

Nicholson Tower – Auditorium

10:35 – 11:40 AM **ACS-IRG AWARDEE SESSION**

Moderator: Stefano Tarantini & Stevie Warner

10:40 – 11:00 AM **The Feasibility of Offering Escalating Incentives to Promote Smoking Cessation Among Adults with Type 2 Diabetes**

Sydney Martinez
Assistant Professor
Department of Epidemiology
The University of Oklahoma Health Sciences Center

11:00 – 11:20 AM **Disparities in Outcomes Among Children with Acute Lymphoblastic Leukemia in Oklahoma, 2005-2019**

Amanda Janitz
Assistant Professor
Department of Epidemiology
The University of Oklahoma Health Sciences Center

11:20 – 11:40 PM **"It Frees Your Body from That Pain Thought": Understanding Cannabis Use for Pain Among Older Residents of Rural Communities**

Julia McQuoid
Assistant Professor
TSET Health Promotion Research Center
Department of Family and Preventive Medicine
The University of Oklahoma Health Sciences Center

THE FEASIBILITY OF OFFERING ESCALATING INCENTIVES TO PROMOTE SMOKING CESSATION AMONG ADULTS WITH TYPE 2 DIABETES

Sydney Martinez[1], Piper Houghton[2], Anne Kapka[1], Deepa Ganesan[1], Afsheen Hasan[1], and Darla E. Kendzor[3]

[1]Department of Biostatistics & Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

[2]Department of Psychology, Oklahoma State University, Stillwater, OK

[3]Department of Family and Preventive Medicine, TSET Health Promotion Research Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Introduction: Providing small financial incentives for smoking abstinence increases cessation rates. However, the effectiveness of incentivizing smoking cessation in populations with chronic diseases, such as type 2 diabetes mellitus (T2DM) is unknown. The feasibility and potential effectiveness of offering escalating abstinence-contingent financial incentives was evaluated among adults with T2DM initiating tobacco cessation treatment.

Methods: Adults with T2DM (N=29) were randomized to contingency management (CM) or usual care (UC) treatment for smoking cessation. Participants completed weekly in-person visits and received a smartphone and remote carbon monoxide sensor to complete twice daily mobile health (mHealth) assessments. Both groups received weekly counseling from 1-week pre-quit date through 4-weeks post-quit date, plus nicotine replacement therapy. CM participants earned gift cards starting at $20 that escalated by $5 per week for biochemically verified abstinence. Both groups earned up to $180 for completing other study assessments. Biochemically-verified abstinence was assessed at the final 4-week post-quit visit. Participants completed exit surveys to assess satisfaction with the program.

Results: Participants were predominantly female (69.0%, n=20) and White (65.5%, n=19), and the mean age was 53.8 (SD=10.3) years. Retention was slightly higher in the CM group, with 85.7% completing the final 4-week post quit visit compared to only 73.3% of the UC group. On average, CM participants completed 58.3% of the twice-daily assessments compared to 50.6% in the UC group. Cessation rates were lower in the CM group compared to UC in both per protocol (33.0% vs 63.6%) and intention-to-treat (28.6% vs 46.6%) analyses, although the differences were not statistically significant. Average total compensation was $268 for the CM group compared to $213 for UC. Overall, 87.5% of participants reported the smartphone as “very easy” or “easy” to use.

Participants also reported ease of use for the study application (87.5%) and remote carbon monoxide sensor (95.8%).
Conclusion: Escalating financial incentives did not result in higher quit rates for the CM group; however, total compensation was high in both groups. Participation and quit rates were high overall, suggesting that incentives may not need to be contingent upon abstinence to increase program engagement and smoking cessation among adults with T2DM.
Funding: Institutional Research Grant number IRG-19-142-01 from the American Cancer Society, National Cancer Institute of the National Institutes of Health P20CA253255, NCI Cancer Center Support Grant/Stephenson Cancer Center Mobile Health Shared Resource P30CA225520, and Oklahoma Tobacco Settlement Endowment Trust (TSET) contract R22-02.
Keywords: Cessation, Disease: Other; mHealth

DISPARITIES IN OUTCOMES AMONG CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN OKLAHOMA, 2005-2019

Amanda E. Janitz[a], Rylee Barber[b], Janis E. Campbell[a], Chao Xu[a], Hanumantha R. Pokala[b], Jessica Blanchard[c], René Y. McNall-Knapp[b]

a. Department of Biostatistics and Epidemiology, Hudson College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, United States
b. Section of Hematology/Oncology, Department of Pediatrics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, United States
c. Center for Applied Social Research, College of Arts and Sciences, University of Oklahoma, Norman, OK, 73072, United States

Background: Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer. While there have been important successes in increasing survival, important gaps remain to understand reasons for disparities in event-free survival (EFS) among underserved populations.
Methods: In collaboration with the OU Health cancer registry and the Oklahoma Central Cancer Registry, we combined registry and electronic health record data to evaluate EFS from ALL. We included children diagnosed with ALL from 2005-2019 prior to age 20 (n=275). We evaluated the relation between 1) race/ethnicity, 2) distance to OU Health, and 3) area deprivation with EFS. We defined EFS as time from diagnosis to relapse, death, or the end of the study period. We evaluated differences in EFS using Kaplan-Meier analysis with the log-rank test. We used the Cox Proportional Hazards Model to estimate hazard ratios (HR) and 95% confidence intervals (CI).
Results: Children with ALL were most commonly diagnosed prior to 5 years of age (45%) and had Pre-B ALL (87%). We observed that 12% of children experienced a relapse and 5% died during remission or induction. Overall, EFS was 82% at 5 years after ALL diagnosis with non-Hispanic (NH) black children having worse, though imprecise EFS compared to NH White children (Adjusted HR: 2.07, 95% CI: 0.80, 5.38). Those residing in census block groups with higher area deprivation had worse EFS compared to those residing in the least deprived areas, though this was also imprecise (2nd quartile HR: 1.51, 3rd quartile: 1.85, 4th quartile: 1.62). We observed no association between distance to OU Health and EFS.
Conclusion: We observed poorer EFS for children from minority and underrepresented populations, though the hazard ratios were not statistically significant. In future analyses, we will further evaluate disparities for urban and rural children and evaluate other cancers, including central nervous system tumors and lymphoma.

“IT FREES YOUR BODY FROM THAT PAIN THOUGHT”: UNDERSTANDING CANNABIS USE FOR PAIN AMONG OLDER RESIDENTS OF RURAL COMMUNITIES

Emily Warner, Desiree Azizoddin, Lance Ford, Hannah Appleseth, David Bradley, Amy Cohn, Michael Businelle, Paul Spicer, Summer Frank-Pearce, Julia McQuoid
Department and University: TSET Health Promotion Research Center, University of Oklahoma Health Sciences Center

Background: Older U.S. adults increasingly report using cannabis to manage chronic pain. Those living in rural areas are less likely than those living in urban areas to receive adequate pain management support given the relative lack of specialist care in rural areas. We aimed to understand how and why some rural Oklahomans use cannabis for pain, including in the context of dual use with opioids. This paper reports findings from a subsample of participants in a mixed methods pilot study with rural Oklahoman adults (n=14) who regularly smoked cigarettes and used at least one other substance, including cannabis, alcohol, opioids, and methamphetamines.
Methods: Participants completed a baseline survey, smartphone-administered ecological momentary assessment (EMA) surveys regarding their substance use over 14 days, and subsequently completed in-depth interviews wherein they explored and discussed mapped geolocations of their own substance use reports.
Findings: Half of participants (n=7; ages 43-65) reported using cannabis to manage chronic pain (i.e., the ‘pain subsample’). Self-reported causes of chronic pain in the pain subsample included injuries and arthritis. Almost all (6/7) reported using cannabis on ≥75% days of data collection. The most frequently reported cannabis use motives were therapeutic or medicinal (90% of use reports) and coping with negative emotions (38% of use reports). Most use reports were for inhaling cannabis smoke (88% of use reports) at home (99% of use reports). Cannabis and opioid use during the same day was relatively common (45% of daily surveys), but did not appear to occur in close temporal proximity of one another. Interview accounts offered nuance to understanding how and why participants used cannabis and other substances for pain. Most described cannabis as modifying their experience of pain sensations and their internal psychological responses to pain, as opposed to eliminating the pain sensation itself. Participants described drawing from a repertoire of substances to manage various aspects of their pain experience including: pain intensity, different qualities of pain (e.g., nerve pain, muscular pain), psychological responses to their pain sensations (e.g., thoughts about pain), and to balance the perceived benefits and risks associated with each substance (e.g., opioids as overly intoxicating and harmful vs. cannabis as less intoxicating and healthy).
Discussion: These findings offer insight into the practices, experiences, and motives of cannabis use among older rural Oklahomans with ‘high impact’ chronic pain and limited access to

comprehensive pain management. Pain management practices with cannabis should be incorporated into pain management provider discussions with patients to address possible risks (e.g., increased risk for falls). Further research should establish the risks and benefits of cannabis use to manage pain for older populations, especially within the context of opioid use.

SESSION I - JOINT PROGRAM SESSION

1:15 – 2:20 PM

JOINT PROGRAM SESSION

Moderators: Resham Bhattacharya & Min Li

1:20 – 1:40 PM

RPRD1B Is a DNA Repair Protein That Suppresses Tumor Formation After Genotoxic Stress

Julio Morales
Department of Neurosurgery
The University of Oklahoma College of Medicine

1:40 – 2:00 PM

Employing Community-Based and MHealth Interventions to Reduce Prostate Cancer Disparities Among African Americans: A Multilevel Approach

Ruosi Shao
Health Promotion Research Center
The University of Oklahoma Health Sciences Center

2:00 – 2:20 PM

Immunogenic Treatment for Metastatic Breast Cancer Using Targeted Carbon Nanotube-Mediated Photothermal Therapy in Combination with Checkpoint Inhibition and Immunoadjuvant

Gabriela Faria
OU Health Stephenson Cancer Center
The University of Oklahoma Health Sciences Center

RPRD1B IS A DNA REPAIR PROTEIN THAT SUPPRESSES TUMOR FORMATION AFTER GENOTOXIC STRESS.

Julio C. Morales, Ph.D.
Department of Neurosurgery and Stephenson Cancer Center
University of Oklahoma Health Science Center
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The genome of the cell is under constant attack from internal and external sources; such as replication stress, reactive oxygen species and ultra-violet light. If not repaired properly the damage from these sources may lead to cell death or mutations that eventually lead to cancer. The most deleterious types of DNA damage that can by introduced into the genome is the DNA double strand break (DSB). DSBs must be repaired in a timely manner, one unrepaired DSB can lead to cell death. Additionally; if left unrepaired, the invasive nature of the free DNA ends of the DSB can result in chromosomal translocations; which is often associated with tumor formation.

There are two major pathways utilized in DSB repair: non-homologous end-joining (NHEJ) and homologous recombination (HR). NHEJ is used throughout the cell cycle and is considered an "error-prone" pathway; as it places no regard to potential genetic material lost when the DSB is made. HR is primarily active during S and G2 phases of the cell cycle, due to presence of a sister chromatid that can be used as a template for repair and is considered "error-free". In order to discover novel regulators of NHEJ repair, we performed a yeast two-hybrid screen utilized the core NHEJ component Ku70 as bait. From this two-hybrid screen, we discovered a novel Ku70 interacting partner: Regulation of nuclear pre-mRNA domain-containing 1B, RPRD1B.

We found that RPRD1B interacts with Ku70 in nuclear extracts of mammalian cells, replicating our yeast-two hybrid screen observations. In order to examine if RPRD1B plays a role in the NHEJ repair pathway, we generated RPRD1B deficient cells using shRNA. We found that RPRD1B deficient cells display increased DSB break formation, chromosomal aberrations, RNA:DNA hybrid formation and sensitivity to genotoxic stress. We also found that NHEJ repair is impaired in RPRD1B deficient cells. In addition to our cell culture observations, we generated a RPRD1B knockout mouse. We found that RPRD1B is essential for mouse development as complete loss resulted in early embryonic lethality. Interestingly, we found that RPRD1B heterozygote mice also displayed increased DSB formation *in vivo*. In addition; similar to *in vitro* experiments, RPRD1B heterozygote mice were also sensitive to whole body exposure to ionizing radiation. 100% of RPRD1B heterozygote mice exposed to ionizing radiation died within ~250 days after exposure. Additionally; upon autopsy, we found thymic tumors in 100% of these radiation exposed RPRD1B heterozygote mice.

In conclusion, we find that RPRD1B is an essential gene that is novel component of NHEJ DSB repair and suppresses tumor formation after radiation exposure. These data suggest that RPRD1B plays an important role in mediating tolerance to DNA damage.

EMPLOYING COMMUNITY-BASED AND MHEALTH INTERVENTIONS TO REDUCE PROSTATE CANCER DISPARITIES AMONG AFRICAN AMERICANS: A MULTILEVEL APPROACH

Ruosi Shao, PhD, Bingjing Mao, PhD, Brianna Fleshmann, BSc, Ivan Flores, MPH, Kimberly Estrada, MPH, David Bradley, MSc, Motolani Ogunsanya, PhD, Summer Frank-Pearce, PhD, Michael Cookson MD, MMHC, Mark Doescher, MD, Michael Businelle, PhD, Adam Alexander, PhD, Jordan Neil, PhD

Worked Performed at Department of Family and Preventive Medicine; Department of Urology; University of Oklahoma Health Sciences Center.

Background: One in six African American (AA) men in the US will develop prostate cancer in their lifetime. Compared with White men, AA men have a 1.7 times higher incidence rate and 2.1 times higher mortality rate from prostate cancer. This disparity is particularly evident in Oklahoma, where the incidence and mortality rates remain higher among AA men than any other racial group. Lack of knowledge about prostate cancer and limited access to prostate-specific antigen (PSA) testing are key contributors to these disparities. Multilevel approaches that employ multiple forms of outreach and intervention (i.e., community- and patient-level) offer promise.

Method: Phase 1 (Community outreach): On June 18, 2022, we hosted the Men's Health Awareness Summit (MHAS) at the Metro Technology Center in Oklahoma City, which involved an (1) educational presentation on prostate cancer and PSA testing by a urologist and (2) a panel discussion from AA prostate cancer survivors. Onsite PSA tests were offered to men who attended. Phase 2 (mHealth intervention): In February 2023, we will recruit AA men from Oklahoma, aged between 55 and 69 (N = 80), to a two-arm randomized controlled trial with 1:1 allocation to intervention (Prostate Cancer Genius App) or control arms (US Preventive Services Taskforce App). Participants can order at-home PSA tests in both arms via their app. The Prostate Cancer Genius App provides access to learning modules, testimonials from prostate cancer survivors with live coaching and peer support, and tailored navigation for PSA screening. The primary outcome is a change in prostate cancer knowledge 30 days post-randomization between arms. We will also explore post-intervention PSA screening rates and identify predictors of screening across both arms.

Results: Phase 1: The MHAS attracted 55 attendees, 67.2% (N = 37) of whom were men, and among which 48.6% (N = 18) opted to complete a PSA test. The total event cost was

$4372.30; organizers spent $79.50 per registered attendee and $118.20 per PSA test (based on male attendees). Phase 2. Preliminary results will be presented, describing ongoing recruitment strategies, accrual rate, baseline participant prostate cancer knowledge, PSA screening intentions, etc.
Conclusion: Multilevel approaches are needed to improve prostate cancer disparities among AA men in Oklahoma. While community-based interventions are an effective strategy to increase awareness and provide access to screening resources, our MHAS was expensive per PSA test completed, and the impact was highly localized. Therefore, we have combined this approach with a mHealth intervention via the first-of-its-kind Prostate Cancer Genius App. Findings from this innovative intervention will assess whether remote navigation can improve knowledge of prostate cancer risk and symptoms and explore whether culturally tailored navigation can increase at-home PSA screening rates.

IMMUNOGENIC TREATMENT FOR METASTATIC BREAST CANCER USING TARGETED CARBON NANOTUBE-MEDIATED PHOTOTHERMAL THERAPY IN COMBINATION WITH CHECKPOINT INHIBITION AND IMMUNOADJUVANT

Gabriela N F Faria[1,3], Alexis Woodward[2], Sampurna Chakraborti[2], Roger Harrison[1]
University of Oklahoma – Chemical, Biological and Materials Engineering[1], Stephenson School of Biomedical Engineering[2], Stephenson Cancer Center[3]

The lack of targeting treatments for triple-negative breast cancer (TNBC) leads to poor prognosis, which spurs the development of novel therapeutic strategies. We have developed a targeted photosensitizer for photothermal therapy (PTT) of solid tumors based on the functionalization of single-walled carbon nanotubes (SWCNT) to annexin A5 (ANXA5): SWCNT-ANXA5 conjugate. SWCNT efficiently convert near-infrared (NIR) light into thermal energy during PTT, aiming to ablate the primary tumor. ANXA5 is a protein that targets externalized phosphatidylserine (PS) on the surface of tumoral cells and tumor vasculature but is absent on the surface of healthy cells.
ANXA5 was produced in *E. coli* and purified by affinity liquid chromatography. The protein is then linked to SWCNT. Previous studies with the EMT6 tumor model, a TNBC model in mice, resulted in excellent results with the combination of anti-PD-1 (three injections, 200 μg) and NIR-irradiation of the tumor for 5 min keeping the tumor surface temperature at 45°C by cycling the laser on and off. The same treatment in 4T1 tumors, a more invasive and less immunogenic TNBC model, resulted in a slightly increased survival but did not generate the tumor-free response seen in EMT6 tumors. Therefore, a more aggressive treatment approach was developed to treat 4T1 tumors, by increasing the PTT temperature to 55°C and adding an immune adjuvant to attract lymphocytes to the tumor environment.
4T1 tumors in BALB c/J female mice were treated with immunotherapy of checkpoint inhibition of anti-PD-1 and immunoadjuvant imiquimod, a TLR-7 agonist. Imiquimod (50 μg) was loaded into an injectable hydrogel for controlled release and injected intratumorally when tumors were ≈3 mm, characterizing day 0. Anti-PD-1 (200 μg) was injected intraperitoneally on days 0, 3, and 8. Tumors were treated on day 4 with PTT 980 nm-near infrared laser at 1 W/cm^2 until tumor surface temperature reached 55°C. Long-term survival tests showed 30% survival of mice for 100 days after tumor inoculation in the complete treatment group, while mice in all the other groups died before day 55, which is evidence of an abscopal effect of the combination therapy, because this tumor model is highly metastatic. Additionally, analysis of splenic cells by

flow cytometry 15 days after PTT showed an increase in helper and cytotoxic T-cells compared to the untreated group only for the complete treatment group.
Future work aims at analyzing the attraction of lymphocytes into the tumor environment by the immunoadjuvant, keeping the tumor at 55°C for prolonged times to improve tumor ablation, and comparing PTT with surgical removal of the tumor, both combined with the immunotherapy, to test the hypothesis of synergist effect of PTT with immunotherapy.

Cancer Biology

CANCER BIOLOGY

Nicholson Tower Auditorium

2:30 – 3:35 PM

SESSION II

Moderators: Deepa Sathyaseelan & Elizabeth Wellberg

2:35 – 2:55 PM

Nnt-As1 Mediated Regulation of Nnt In Ovarian Cancer

Shailendra Dwivedi
Stephenson Cancer Center

2:55 – 3:15 PM

Circular Rna Anapc7 Inhibits Tumor Growth and Ameliorates Muscle Wasting Via Phlpp2–Akt–Tgf-B Signaling Axis in Pancreatic Cancer

Jingxuan Yang
Department of Medicine
The University of Oklahoma Health Sciences Center

3:15 – 3:35 PM

Tumor Targeted Immuno-Liposomal Rd3 Delivery Diverts Mir Programing in Rd3 Null Aggressive and Progressive Neuroblastoma Cells

Sreenidhi Mohanvelu
Department of Biostatistics and Epidemiology
The University of Oklahoma Health Sciences Center

3:40 – 4:45 PM

SESSION III

Moderators: Ralf Janknecht & Jerry Wu

3:40 – 4:05 PM

Exosomal Uca1 Reprograms Glucose Metabolism in Peritumoral Fibroblasts in Ovarian Cancers

Revathy Nadhan
Stephenson Cancer Center

4:05 – 4:25 PM

Proteomic Studies of Interactions Between Drug-Resistant and Drug-Sensitive Cancer Cells

Zongkai Peng
Department of Chemistry and Biochemistry
The University of Oklahoma

4:25 – 4:45 PM

The Role of Necroptosis Associated Chronic Inflammation in The Development of Liver Cancer

Ramasamy Selvarani
Department of Biochemistry and Molecular Biology
The University of Oklahoma Health Science Center

NNT-AS1 MEDIATED REGULATION OF NNT IN OVARIAN CANCER

Shailendra Kumar Dhar Dwivedi[1,2], Resham Bhattacharya1,[2]

1. Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, USA
2. Peggy and Charles Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73104, USA

Among the malignancies affecting the female reproductive tract, epithelial ovarian cancer is the leading health concern. A woman's chance of getting ovarian cancer (OvCa) is about 1 in 78, and her chance of dying from it is 1 in 108. Despite improvements in therapy, mortality from OvCa is predicted to significantly increase by 2040 (American Cancer Society). Unfortunately, most of the ongoing OvCa research has largely been focused on a few previously known targets hence identification and development of novel targets is a priority.

Long non-coding RNAs (lncRNAs) are non-protein-coding transcripts longer than 200 nucleotides. Emerging evidence suggests that lncRNAs are associated with cancer progression and are involved in cell death resistance, invasion, proliferation, gene deregulation, and genomic instability. Interestingly, Genomic analyses of OvCa patient samples from the Cancer Genome Atlas (TCGA) reported amplifications of the 5p13.2 locus, and our further analysis revealed that this locus encodes for the lncRNA, NNT antisense RNA 1 (NNT-AS1). Importantly, in our current research, we established that NNT-AS1 is expressed at significantly higher levels in OvCa than in normal ovarian tissue and positively correlates with nicotinamide nucleotide transhydrogenase (NNT) mRNA levels in these samples. This finding was further supported by the NNT-AS1 and NNT expression in OvCa cell lines. NNT is a dimeric proton pump that resides in the inner mitochondrial membrane of eukaryotic cells and contributes to ~45% of the total NADPH pool within the mitochondria. Intriguingly, we found a unidirectional regulation of NNT through NNT-AS1 by regulating its mRNA stability. Furthermore, inhibition of NNT-AS1 or NNT in HGSOC cell lines decreases proliferation, invasion, and clonal growth, which is mediated via NNT. Silencing either NNT-AS1 or NNT resulted in a significant increase in total and mitochondrial reactive oxygen species (ROS), leading to apoptosis. These findings further confirm the significance of NNT-AS1 and NNT in ovarian cancer progression.

Importantly unlike cellular signaling pathways that incorporate signal amplification cascades lncRNAs **(a)** function at absolute expression levels and are **(b)** expressed at a relatively low level in a tissue-specific manner, this makes them ideal targets for targeting cancer cells precisely by using lower concentrations of oligonucleotide targeted to lncRNA, thereby avoiding toxicities that occur with the other oligonucleotide therapies. Further studies in this direction will lead to the identification and development of novel targets for drug resistance OvCa,

Acknowledgment: *This research is supported by the Oklahoma Center for the Advancement of Science and Technology (OCAST) to SD. Services from the Stephenson Cancer Tissue Pathology Core are humbly acknowledged.*

CIRCULAR RNA ANAPC7 INHIBITS TUMOR GROWTH AND AMELIORATES MUSCLE WASTING VIA PHLPP2–AKT–TGF-B SIGNALING AXIS IN PANCREATIC CANCER

Jingxuan Yang

Cancer cachexia is the leading cause of death for cancer patients at the late stage, with the highest prevalence in pancreatic cancer. There is an urgent need to understand the mechanisms of cancer cachexia for developing novel diagnoses and therapeutics. ZIP4 promotes pancreatic cancer progression by regulating oncogenic miR-373, and perturbation of circular RNAs (circRNAs) is associated with cancer aggressiveness. We aimed to identify circRNAs that are involved in pancreatic cancer cachexia and decipher the underlying mechanism. Differentially expressed circRNAs and potential targets of miRNA were identified through in-silico analysis. The molecular mechanisms of circRNA/miRNA interaction were determined by RNA immunoprecipitation, biotinylated miRNA pulldown, and luciferase reporter assays. The function of circRNA and the interaction between circRNA and ZIP4 signalling were examined in human pancreatic cancer cells, 3D spheroids and organoids, orthotopic xenograft mouse model and human specimens. The skeletal muscles and adipose biopsies were analyzed by histology. We identified circANAPC7 as a sponge for miR-373, which inhibited tumor growth and cancer cachexia in vitro and in vivo. Mechanistic studies showed that PHLPP2 is a downstream target of ZIP4/miR-373. CircANAPC7 functions through PHLPP2 mediated dephosphorylation of AKT, thus suppressing cancer cell proliferation by downregulating Cyclin D1 and suppressing cachexia via decreasing the secretion of TGF-β. We further demonstrated that PHLPP2 induces dephosphorylation of CREB, a zinc-dependent transcription factor activated by ZIP4, thereby forming a CREB/miR-373/PHLPP2 feed forward loop to regulate tumor progression and cancer cachexia. This study identified circANAPC7 as a novel tumor suppressor, which functions through the CREB/miR-373/PHLPP2 feed forward loop, leading to AKT dephosphorylation and Cyclin D1 and TGF-β downregulation to inhibit tumor growth and improve cachexia in pancreatic cancer.

TUMOR TARGETED IMMUNO-LIPOSOMAL RD3 DELIVERY DIVERTS MIR PROGRAMING IN RD3 NULL AGGRESSIVE AND PROGRESSIVE NEUROBLASTOMA CELLS.

Sreenidhi Mohanvelu, Dinesh Babu Somasundaram, and Natarajan Aravindan
Department of Radiation Oncology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

Therapy defiant progressive neuroblastoma (NB), the most common extracranial solid tumor in children is almost always fatal. Recently, we showed that Retinal Degeneration Protein 3 (RD3) is constitutively expressed in healthy fetal tissues and is lost linearly in the progression of NB. Beyond iterating its association to advanced disease stage and poor survival outcomes in NB patients, we also demonstrated its function in NB pathogenesis and therapy resistance. Functionally, RD3-loss deregulates NB cell differentiation and prompts lineage transformation. Here, we investigated whether NB-targeted reinstatement of RD3 reprogram the genetic blueprint of the RD3 null cells and impede tumor evolution. RD3 knocked out (stable transfection) bone-marrow derived NB (metastasis) cells from patients during diagnosis (Dx, CHLA-42) or with progressive disease (PD, SH-SY5Y) cells were treated with/without RD3-immunoliposomes (RD3-IL). For this, full-length RD3 protein was incorporated into the GD2 (for NB-specificity) labelled liposomes. miRNome modifications were assessed using Nanostring ncounter miRNome expression assay and analyzed with nSolver software. Differential expression analysis coupled with stringent criteria (≥2-fold up/down modulation) calculation identified distinctive upregulation of 15 miRs in CHLA-42 (Dx) and 74 miRs in SH-SY5Y (PD) cells. Interestingly, miR-Walk bioinformatics identified that RD3-IL modified miRs both in Dx or PD cells (despite the distinctive miR profiles), majorly converge in regulating key molecular (TGFβ, Hippo, WNT, NOTCH, NFkB, JAK-STAT, FOXO, mTOR) pathways those regulate EMT, CSC stemness maintenance, self-renewal, therapy resistance, dedifferentiation, and metastasis. Evidently, RD3-IL treatment response was significant in PD cells with upregulation 55 (of 74) miRs that were downregulated in Dx cells, as well converge on the cellular functions mentioned above, and further regulates stem cell lineage, chemosensitization and anti-tumor immune response. Together, the results demonstrate that RD3-IL treatment rearrange miR profile in high-risk and in the progressive NB cells *in vitro*, those impede NB progression and metastatic state. Further, our data unveiled that tumor targeted RD3 delivery to the PD cells exclusively regulate NB cell dedifferentiation, lineage transformation, CSC stemness maintenance, and self-renewal capacity. These outcomes identify a new and improved molecular targeted and tumor targeted maintenance therapy for progressive NB.
Funding: DoD and OCAST

EXOSOMAL UCA1 REPROGRAMS GLUCOSE METABOLISM IN PERITUMORAL FIBROBLASTS IN OVARIAN CANCERS

Revathy Nadhan, Ji Hee Ha, Muralidharan Jayaraman, Srishti Kashyap, Danny N. Dhanasekaran

Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

Presenting Author E-mail: Revathy-Nadhan@ouhsc.edu

A co-ordinated signaling between the tumor cells and components of the tumor stroma regulates the process of tumor genesis and progression. Exosomes have been identified as cardinal mediators that facilitate the transfer of numerous oncogenic factors amongst the cellular components of the tumors and hence, can ideally be targeted for therapy. Long non-coding RNAs (lncRNAs) have been recently explored for their significant roles in regulating diverse tumorigenic phenotypes. Hence, we analyzed the ovarian cancer cell derived exosomal lncRNAs to identify the candidate that drives the ovarian cancer progression, which can serve as a prominent therapeutic target. A lncRNA array of the exosomes derived from a panel of high grade serous ovarian cancer cell lines identified that UCA1 (Urothelial Cancer Associated 1) is the most abundant exosomal lncRNA. Correspondingly, exosomes from patient derived ovarian cancer cells as well as from ascites of ovarian cancer patients exhibited upregulation of exosomal UCA1. PKH-67 labelling of the ovarian cancer cell derived exosomes revealed the exosomal uptake by MRC5 fibroblast cell line. There are reports on metabolic reprogramming of stromal fibroblasts through paracrine signaling. Hence, we inspected whether transfer of exosomal UCA1 from the ovarian cancer cells to the stromal fibroblasts would reprogram the glucose metabolism in the latter that might contribute to tumorigenesis. Agilent Seahorse glycolytic stress assay reveal that exosomal UCA1 enhances glycolysis in stromal fibroblasts. This was further corroborated by the levels of key glycolytic enzymes in the stromal fibroblasts, post exosomal UCA1 transfer. Thus, our study serves as a significant indication that exosomal UCA1 promotes tumorigenic signaling through metabolic reprogramming of the stromal fibroblasts. The role of UCA1 in promoting diverse tumorigenic phenotypes in different cancers have already been reported. Thus, the current data is suggestive of targeting UCA1 as a precision cancer strategy to target both the cancer cells and stromal cells in ovarian cancers.

This research was supported by the Department of Defense Ovarian Cancer Research Program Awards W81XWH-18-1-0066, W81XWH-22-1-0415, Stephenson Cancer Center, and the Oklahoma Tobacco Settlement Endowment Trust as well as the shared resources support from the NIGMS grant P20 GM103639, the NCI grant P30 CA225520.

PROTEOMIC STUDIES OF INTERACTIONS BETWEEN DRUG-RESISTANT AND DRUG-SENSITIVE CANCER CELLS

Zongkai Peng, Dr. Nagib Ahsan*, Dr. Zhibo Yang*
Zongkai.Peng-1@ou.edu
University of Oklahoma, Norman

Introduction: In the US, colorectal cancer is the third cancer-related death. Irinotecan (IR), the current treatment drug for colon cancer, with its active form metabolite SN-38 could inhibit the enzyme needed for DNA replication and transcription.[1] However, the efficacy of chemotherapy is limited by the drug resistance gained from the tumor. Understanding mechanisms of drug resistance is critical for fundamental research and clinical treatment of cancers; however, the exact mechanisms are not fully understood. Reported studies indicate that not only drug-resistant cells themselves show resistance to chemotherapy, but their communications with drug-sensitive cells helps the later ones to gain drug resistance in the tumor microenvironment.[2] Particularly, our previous studies show that, through interactions with drug-resistant cells, drug-sensitive cancer cells acquired significantly increased drug resistance and exhibited drastically altered metabolites.[3] To better understand the interactions between drug-resistant and drug-sensitive cells at protein levels, we performed quantitative proteomics studies and analyzed the global protein expression in different cell models. In the control experiments, we performed monoculture using drug-resistant and drug-sensitive cells. In coculture models, we used both direct and indirect co-culture systems. We then performed quantitative bottom-up proteomics of these cell systems to understand the enhanced chemoresistance of drug-sensitive cells through their communications with drug-resistance cells.

Methods: The colon carcinoma HCT116 cell line was treated with low concentration IR (1 μM) for 20 days to obtain the drug-resistant cell line (IRI-HCT116). Using the same protocols, the GFP label cell line (IRI-HCT116-GFP) was also prepared, allowing for FACS cell sorting in the direct coculture system. These two cell lines were used in the control (monoculture cells) and two different co-culture models.

Indirect co-culture: Drug-sensitive cell line (HCT116) and drug-resistant cell line (IRI-HCT116) were co-cultured in 6-well plates, in which these two different cell lines were separated using TransWell permeable supports (0.4 μm pore size). After 72 h co-culture, the insert was removed, and the drug-sensitive cell (InCo-HCT116) were harvested for quantitative proteomic analysis.

Direct co-culture: GFP labeled drug-sensitive cell line (HCT116-GFP) and IRI-HCT116 were mixed and cocultured in the same wells of 6-well plates for 72h. Then, HCT116-GFP cells (DiCo-HCT116-GFP) were collected using FACS for quantitative proteomic analysis.

All samples were subjected to protein denature, alkylation, trypsin digestion, de-saltation, and tryptic peptide enrichment. One microgram BSA (23225, Thermo Scientific) was spiked in each sample/replicate before the digestion steps. The obtained peptides were used for LC-MS/MS analysis using Thermo Q-Exactive Plus HFX Hybrid Orbitrap mass spectrometer coupled to the Dionex3000 nanoLC system.

Preliminary data:Drug resistance analysis and GFP labeled cell line evaluation:
Label-free quantitative proteomic analysis of the 12 HCT116 cell samples (i.e., HCT116 (H), HCT116-GFP (GH), IRI-HCT116 (IR) and IRI-HCT116-GFP (GIR) with 3 replicates for each group) were analyzed, and a total of 2542 unique protein groups were successfully identified and quantified.
The principal component analysis (PCA) showed high reproducibility among replicates. As expected, GFP labeling has no significant influence on global protein expression, because close clustering was observed for HCT116 vs HCT116-GFP groups (Control) and IRI-HCT116 vs IRI-HCT116-GFP groups (drug-resistant). However, a significant difference was observed between the control and drug-resistant group samples (Figure 1).

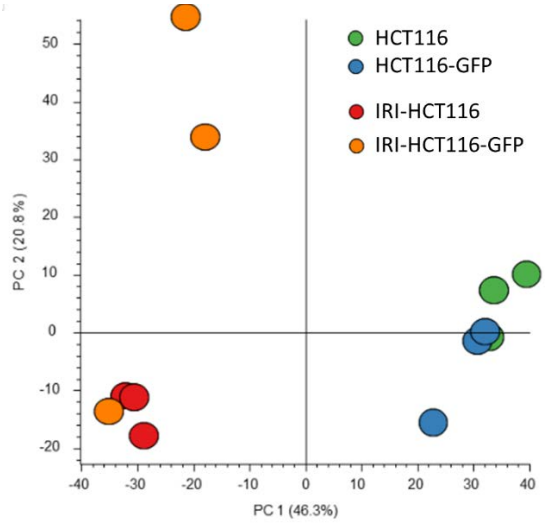

Figure 1. PCA of total the protein abundance of each sample
The abundances of multiple P53 signaling pathway proteins, such as CDK1A and CDK4, significantly increased in both drug-resistant cell lines compared with the control groups, indicating a strong association of P53 signaling pathways in the drug resistance mechanism. In the sphingolipid signaling pathway, we found ASAH1 and CERS2 were abundant in drug-resistant cell lines (Figure 2). These two proteins affect the sphingolipid and ceramide synthesis, indicating that sphingolipid and ceramide may play an important role in IRI drug resistance.

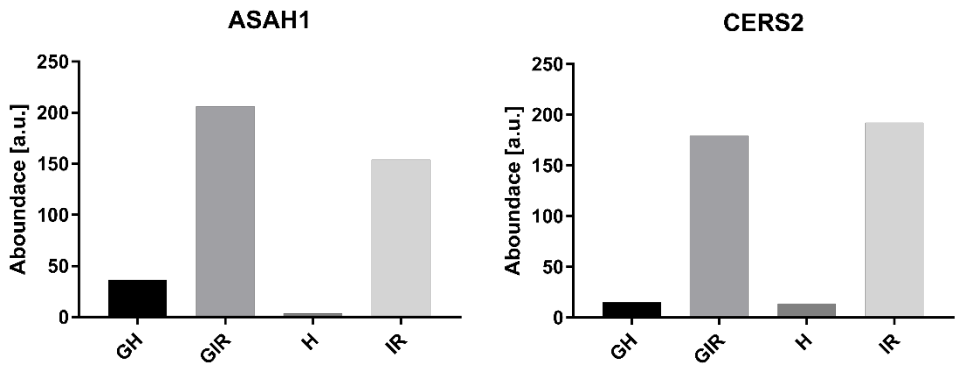

Figure 2. ASAH1 and CERS2 protein abundance in 4 groups of cells

Direct co-culture and indirect co-culture:

Our studies were focused on proteomics of drug-sensitive cells affected by drug-resistant cells. In total, 1983 proteins were identified in both direct co-culture and indirect co-culture drug-sensitive cells (Figure 3). Among them, 297 proteins were significantly changed after direct co-culture and 160 proteins for indirect co-culture. There are 58 proteins significantly expressed (up- or down-regulation) in both systems, and these common proteins could be responsible for chemoresistance signaling. Interestingly, some proteins (e,.g., SRP14 and ECHDC1) only have significantly altered expression in direct co-culture, and these proteins may only participate in the short-distance cell-cell communication. More data will be processed to understand cell-cell communication. Particularly, we will conduct single-cell proteomics studies to obtain more information for better understanding cell-cell communication.

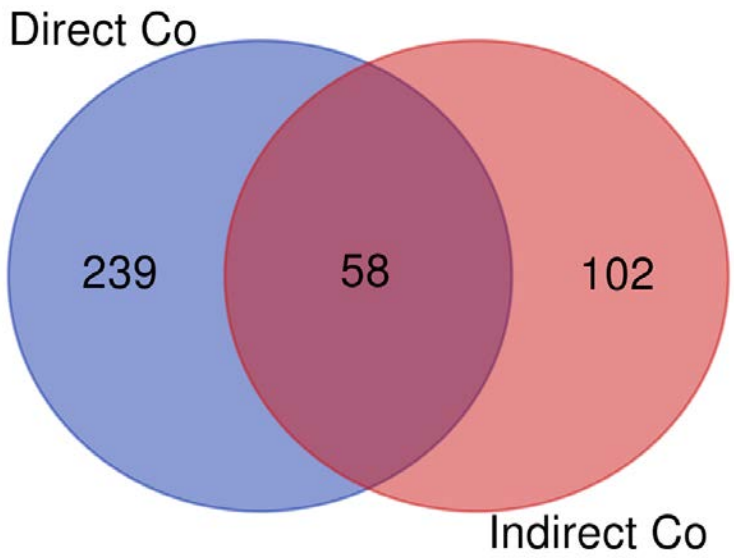

Figure 3. Significantly changed protein in Direct co-culture and Indirect co-culture systems. (Fold Change> 1.5; P-value < 0.05)

References:

1. Slatter J G, et al; *Drug Metab. Dispos.*; 1997, 25 , 1157–1164.
2. B. L. Brucher and I. S. Jamall, *Cell Physiol Biochem*, 2014, 34, 213-243.
3. Chen, X., Peng, Z., Yang, Z.; *Chem. Sci.,* 2022, 13, 6687-6695.

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Research Council of the University of Oklahoma Norman Campus

THE ROLE OF NECROPTOSIS ASSOCIATED CHRONIC INFLAMMATION IN THE DEVELOPMENT OF LIVER CANCER

Ramasamy Selvarani[1], HoangVan MichelleNguyen[2], Sathyaseelan S. Deepa[1], and Arlan Richardson[1]

[1]Department of Biochemistry & Molecular Biology, [2]Department of Nutritional Sciences, University of Oklahoma Health Sciences Centre, Oklahoma City, Oklahoma

Background: Chronic inflammation is believed to play a major role in aging and various age-related disease such as cancer, diabetes, cardiovascular disease, and neurodegeneration. My research is focused on the role inflammation plays in hepatocellular carcinoma (HCC). Liver injury caused by either Hepatitis C viral infection, alcoholism, or high-fat diets/obesity can lead to HCC, in which the incidence is correlated with the severity of inflammation. HCC arises through stages of non-alcoholic fatty liver (NAFLD)/steatosis and progresses to chronic inflammation and NASH, fibrosis. Although chronic inflammation is believed to play an important in age-related diseases such as HCC, the mechanism responsible for the increase in inflammation leading to HCC is unknown. Necroptosis is a pathway of regulated necrosis, which plays a major role in inflammation, and we have shown necroptosis increases with age. Necroptosis is initiated when necroptotic stimuli (e.g.TNFα, ROS) sequentially activate Ripk1, Ripk3, Mlkl proteins through phosphorylation. Phosphorylated Mlkl binds to and disrupts the plasma membrane of cells releasing DAMPs, which bind to immune cells and trigger the release of proinflammatory cytokines leading to inflammation.

Objective: To develop mouse models in which necroptosis can be induced in specific tissues and to determine the physiological impact of inducing necroptosis on a tissue/animal.

Methods: We generated Ripk3 and Mlkl knock-in (KI) mouse models using a transgene containing the cDNA for Ripk3 or Mlkl with a stop cassette flanked by loxp sites to either the Ripk3 or Mlkl cDNA, which is inserted into the Rosa26 locus through CRISPR/Cas9 repair. We crossed KI female to albumin-Cre male mice to generate hepatic KI mice that express Ripk3 or Mlkl specifically in hepatocytes in the liver, i.e., albRipk3-KI or albMlkl-KI mice.

Results: The transgenes for Ripk3 or Mlkl are expressed only in liver and the expression of these two genes is 10- or 4-fold higher in the albRipk3-KI or albMlkl-KI mice, respectively compared to control mice. Treating either albRipk3-KI or albMlkl-KI mice with CCl_4 resulted in increased necroptosis, inflammation, and liver damage in albRipk3-

KI or albMlkl-KI mice compared to control mice. In addition, we found that old (18 months) albRipk3-KI or albMlkl-KI mice have increased necroptosis and inflammation in the liver compared to control mice. We are now using these mice to test the impact of necroptosis derived inflammation on the development of chronic liver disease and HCC in mice fed a high-fat Western diet.

Cancer Prevention & Control

CANCER PREVENTION & CONTROL

Nicholson Tower – Room A

2:30 – 3:35 PM

SESSION II

Tobacco Use and Cessation

Moderator: Darla Kendzor

2:35 – 2:50 PM

Effects of a Nicotine Warning Label and Vaping Cessation Resources on Young Adults Perceptions of Pro-Vaping Instagram Influencer Posts

Erin Vogel
TSET Health Promotion Research Center; Department of Pediatrics
The University of Oklahoma Health Sciences Center

2:50 – 3:05 PM

Disparities in Joint Trajectories of Cigarette and E-Cigarette Use Across Sexual Orientation Groups of Young Adult Men and Women in The Us

Katelyn Romm
TSET Health Promotion Research Center; Department of Pediatrics
The University of Oklahoma Health Sciences Center

3:05 – 3:20 PM

Gender-Specific Motives and Barriers for Tobacco Smoking Cessation in Lao Peoples Democratic Republic

Shweta Kukarni
Department of Biostatistics and Epidemiology
The University of Oklahoma Health Sciences Center

3:20 – 3:35 PM

E-Cigarette Aerosols Induce the Expression of Nrf2 and Its Downstream Targets in Human Bronchial Cells and Modulate Inflammatory Markers

Vengatesh Ganapathy
Department of Otolaryngology Head and Neck Surgery
The University of Oklahoma Health Sciences Center

3:40 – 4:45 PM

SESSION III

Cancer Survivorship

Moderator: Paul Spicer

3:40 – 4:00 PM

Exploring Bioimpedance Phase Angle Trajectories After High-Frequency Prehabilitation for Pancreaticoduodenectomy

Abby Cha
Cancer Rehabilitation Research
Stephenson Cancer Center

4:00 – 4:15 PM

Peripheral Neuropathy Phenotyping in Gynecologic Cancers Suggests Motor Predominance

Elizabeth Hile
Rehabilitation Sciences – Cancer Rehabilitation
The University of Oklahoma Health Sciences Center

4:15 – 4:30 PM

Longitudinal Application of Data-Driven Modelling to Analyze Heel-Toe Plantar Pressure Trajectories in Women with Gynecologic Cancer During Neurotoxic Chemotherapy

Hazem Refai (Ahmed Elsebaay)
Electrical and Computer Engineering
The University of Oklahoma

4:30 – 4:45 PM

Artificial Intelligent Framework Using Plantar Pressures to Distinguish Clinical Peripheral Neuropathy Phenotypes in Women's Cancers

Kangjun Seo
Electrical and Computer Engineering
Department of Otolaryngology Head and Neck Surgery
The University of Oklahoma

EFFECTS OF A NICOTINE WARNING LABEL AND VAPING CESSATION RESOURCES ON YOUNG ADULTS' PERCEPTIONS OF PRO-VAPING INSTAGRAM INFLUENCER POSTS

Erin A. Vogel,[1,2] Jennifer B. Unger,[1,2,3] Julia Vassey[1], Jessica L. Barrington-Trimis[1,2,3]

[1]Department of Population and Public Health Sciences, University of Southern California Keck School of Medicine

[2]Institute for Addiction Sciences, University of Southern California

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Presenting author's current affiliation: TSET Health Promotion Research Center, University of Oklahoma Health Sciences Center; erin-vogel@ouhsc.edu

Background: Influencers (i.e., trend-setting individuals who are often compensated for promoting products on social media) advertise nicotine/tobacco products on Instagram. Warning labels and cessation resources may help mitigate effects of influencer posts on young adults.

Methods: Young adults (N=2,179, 53.0% women, 45.1% Hispanic, 14.9% with regular past-month vaping) participating in a prospective cohort study in Southern California completed an experiment (Nov. 2021-April 2022). Participants viewed three purported Instagram influencer posts related to nicotine vaping, designed for this study. Participants were randomized to view posts with a nicotine warning label ("label"), vaping cessation resources ("link"), both ("L&L") or neither ("control"). Participants then reported perceptions of the influencers; product use intentions, susceptibility, and expectancies, harm perceptions; and vaping perceptions and intentions.

Results: L&L increased perceptions of influencers as more honest (M=47.9, SD=23.7), trustworthy (M=39.7, SD=21.7), and informed (M=42.6, SD=23.3) compared to link or control. Labels (without a link) produced perceptions of the influencers as more honest (M=47.0, SD=23.7) and informed (M=39.9, SD=22.2) and less popular (M=41.5, SD=22.8) compared to link and control conditions. More control condition participants (53.3%) were susceptible to product use, compared to the link (45.5%) and L&L (46.6%) conditions. Post features did not affect brand use intentions, expectancies, harm perceptions, desire to quit vaping, quit-vaping self-efficacy, or having a goal to quit vaping (p-values>.056).

Conclusions: Young adults perceived Instagram influencers promoting vaping products as more honest, trustworthy, and informed when the influencers provided a nicotine warning label and a link to vaping cessation resources on their posts. The warning label and link decreased susceptibility to product use. Nicotine warning labels and nicotine cessation resources are necessary tools in counteracting effects of influencer advertising; however, they may have the unintended side effects of increasing trust in the influencer and effectiveness of future

nicotine/tobacco product advertisements. Research is needed to identify messages that promote nicotine cessation, which could then be made mandatory additions to posts that promote nicotine/tobacco products.

Funding: National Cancer Institute (U54 CA180905, P30CA14089, R01CA226917), National Institute on Drug Abuse (K01DA042950)

DISPARITIES IN JOINT TRAJECTORIES OF CIGARETTE AND E-CIGARETTE USE ACROSS SEXUAL ORIENTATION GROUPS OF YOUNG ADULT MEN AND WOMEN IN THE US

Authors: Katelyn F. Romm,[1,2] Amy M. Cohn,[1,2] Yan Wang,[3] & Carla J. Berg[3,4]
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[2]Department of Pediatrics, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[3]Department of Prevention and Community Health, Milken Institute School of Public Health, George Washington University, Washington, DC, USA
[4]George Washington Cancer Center, George Washington University, Washington, DC, USA
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Background: Disparities in tobacco use prevalence continue to impact sexual minority young adults (SMYAs). Cigarettes and e-cigarettes are the most popular tobacco products used by YAs. Research is needed to identify longitudinal trajectories of cigarette and e-cigarette use in subgroups of SMYAs.
Methods: We analyzed data from 2,809 men (n=1,235; M_{age}=25.5; 8.0% bisexual, 12.7% gay; 36.4% racial/ethnic minority) and women (n=1,574; M_{age}=24.64; 23.8% bisexual, 5.9% lesbian; 35.3% racial/ethnic minority) in a 2-year, 5-wave longitudinal study (2018-2020), including wave 1 demographics and waves 1-5 past 6-month cigarette and e-cigarette use days. We conducted repeated measures latent profile analysis to identify profiles of cigarette and e-cigarette use trajectories, then multinomial logistic regression analyses controlling for age, race/ethnicity, and city of residence, among men and women, separately.
Results: Six profiles were identified: stable low-level (LL) cigarette and e-cigarette use (66.6%), stable LL cigarette use and either high-level (HL; 12.2%) or decreasing (6.2%) e-cigarette use, stable mid-level (ML) cigarette use with LL e-cigarette use (6.2%), stable HL cigarette use with LL e-cigarette use (4.5%), and decreasing HL cigarette use and stable HL e-cigarette use (4.2%). Using stable LL cigarette and e-cigarette use as the referent group, gay (vs. heterosexual) men less likely displayed stable LL cigarette with stable HL e-cigarette use, and bisexual (vs. heterosexual) women more likely displayed: a) stable LL cigarette with stable HL e-cigarette use; b) stable LL cigarette with decreasing HL e-cigarette use; or c) stable HL cigarette with stable LL e-cigarette use. There were no differences between heterosexual and bisexual men or heterosexual women and lesbian women, respectively, on any use trajectories.
Conclusions: Bisexual women displayed problematic trajectories (i.e., continued HL cigarette or e-cigarette use, e-cigarette experimentation). Few differences emerged among subgroups of men. Tailored interventions and messaging campaigns could curtail tobacco-related disparities among SMYA men and women, particularly bisexual women.

Acknowledgement of Funding: This work was supported by the US National Cancer Institute (R01CA215155-01A1; PI: Berg). Drs. Romm and Cohn are supported by Oklahoma Tobacco Settlement Endowment Trust (TSET) contract #R22-03 and the National Cancer Institute grant awarded to the Stephenson Cancer Center (P30CA225520).

GENDER-SPECIFIC MOTIVES AND BARRIERS FOR TOBACCO SMOKING CESSATION IN LAO PEOPLE'S DEMOCRATIC REPUBLIC

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BACKGROUND: Tobacco smoking represents a major public health problem in the Lao People's Democratic Republic (Lao PDR). The burden of cancer in Lao PDR is amongst the highest in Southeast Asia. However, there are very few tobacco cessation programs available there. To improve the potential effectiveness of future tobacco treatment programs, this qualitative study of Lao current or past smokers aims to identify gender-specific motives and barriers to quitting smoking.

METHODS: We conducted focus group discussions (FGDs) with 43 smokers (27 men and 16 women) in total at two hospitals, Setthathirath Hospital in Vientiane Capital and Champasak Hospital in Champasak Province. We used purposive sampling to select a diverse sample with regard to age, gender, and urban/rural residence. Interviews were voice recorded and transcribed verbatim. Data were analyzed using thematic content analysis aided by the MAXQDA program. Codes and themes related to smoking cessation behavior were based on theoretical constructs of the Phase-Based Model (PBM). We used the interactive quote matrix feature to understand gender-specific themes.

FINDINGS: Regarding gender-specific patterns of smoking, women tended to smoke at home while men tended to smoke while socializing with friends (particularly drinking with friends). Some of the PBM-related motives to quit identified among all smokers included the need to protect family's health, the need to save money, the need to prevent the negative health consequences of smoking such as cancer and respiratory disorders and maintaining the government's employment status. Women who smoked additionally identified the presence of a smoke-free environment and personal determination as motives to quit. The PBM-related barriers to quitting differed across gender. Barriers identified by female smokers include a lack of awareness about the hazards of smoking, the influence of friends, and the presence of wrong mindsets about smoking (e.g., quitting is impossible). Meanwhile, male smokers identified severe cravings, ease of buying cigarettes, having a job at night shift, and the habit of smoking while drinking as the main barriers to quitting.
INTERPRETATION: The analysis identified the gender-specific motives and barriers to quitting smoking in Lao PDR. These findings can guide the design of tobacco treatment interventions tailored to smokers' gender.
Keywords: smoking cessation, tobacco treatment, cancer prevention, Lao PDR
Funding: This study was supported by grants (5R21CA253600-02 and 3R21CA253600-02S1) from the US National Cancer Institute (NCI) and Fogarty International Center. SK, TNL, MSB, and TCB are also supported in part by an NCI Cancer Center Support Grant (P30CA225520, awarded to the University of Oklahoma Stephenson Cancer Center) and a grant from the Oklahoma Tobacco Settlement Endowment Trust (R23-02). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.
Acknowledgment: We would like to thank staff of the Ministry of Health of Lao PDR, National Center for Laboratory and Epidemiology of Lao PDR, Setthathirath Hospital, and Champasak Hospital for supporting data collection.
Conflicts of Interest: All authors declare no conflict of interest.

E-CIGARETTE AEROSOLS INDUCE THE EXPRESSION OF NRF2 AND ITS DOWNSTREAM TARGETS IN HUMAN BRONCHIAL CELLS AND MODULATE INFLAMMATORY MARKERS

Vengatesh Ganapathy[1], Daniel Brobst[1], Jimmy Manyanga[1,2], Balaji Sadhasivam[1], Mayilvanan Chinnaiyan[1] and Lurdes Queimado[1-3]

Departments of [1]Otorhinolaryngology and [2]Cell Biology; [3]TSET Health Promotion Research Center, Stephenson Cancer Center, The University of Oklahoma Health Sciences Center, Oklahoma.

Background: In recent years, the use of electronic cigarettes (e-cigs) has increased exponentially among both adolescents and young adults worldwide. E-cigs are perceived by users as a safer alternative to traditional cigarettes. Reports show that e-cig users are more likely to develop respiratory diseases. E-cig aerosols contain significantly fewer chemicals than cigarette smoke, but they still contain harmful and potentially harmful components including reactive oxygen species (ROS). Our previous *in vitro* studies have shown that e-cig aerosols induce oxidative stress. However, the molecular mechanisms underlying e-cig induced oxidative stress and alteration of immune response are unknown.

Aims: To evaluate whether e-cig aerosols alter the expression of NRF2 and its downstream targets and modulate inflammatory markers in bronchial cells.

Methods: Human normal bronchial epithelial cells (Nuli1) were exposed to e-cig aerosol extracts every other day for 2 weeks. E-cig aerosol extracts were prepared from two different e-cig brands with similar e-liquids (18 mg/ml of nicotine; tobacco flavor). Standard tobacco smoke extracts were used as a positive control. Quantification of 37 key biomarkers of inflammation was performed on Nuli1 cell extracts and media using a BioRad multiplex kit. The expression of NRF2, KEAP1, HMOX1, catalase, TLR4, and IRF7 proteins was quantified by Western blotting. Data were analyzed by Student's t-test.

Results: Exposure to e-cig aerosol extracts resulted in increases in NRF2, HMOX1, and catalase proteins and decreases in KEAP1 protein. A significant increase in TLR4 and IRF7 proteins was also consistently observed after exposing bronchial cells to e-cig aerosols. Significant changes in cytokines were observed after exposure to e-cig aerosol extracts, including a significant decrease in the expression of IL8, IL10, IL22, IFN-α2 and sTNF-R2 proteins.

Conclusion: Chronic exposure to e-cig aerosols causes significant changes in the expression of NRF2 and its downstream targets. The decrease in KEAP1 and the increase in NRF2 could modulate oxidative stress through upregulation of HMOX1 and catalase. Upregulation of HMOX1 has been shown to modulate inflammation and the immune response by altering cytokine levels. IRF7 has been shown to alter inflammatory responses via the TLR4 signaling pathway. Our data suggest that e-cig use induces the expression of the master regulator of

oxidative stress, upregulating its downstream targets, and altering the immune response, which may have significant biological and clinical implications.

Grant support: This work was supported by a seed grant from the Health Promotion Research Center (Ganapathy), the National Institutes of Health/National Cancer Institute (R01CA242168), and the Oklahoma Tobacco Settlement Endowment Trust.

EXPLORING BIOIMPEDANCE PHASE ANGLE TRAJECTORIES AFTER HIGH-FREQUENCY PREHABILITATION FOR PANCREATICODUODENECTOMY

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OU Health Stephenson Cancer Center [1]Cancer Rehabilitation Research and [2]Cancer Rehabilitation Clinic; [3]The University of Oklahoma Department of Health Exercise & Sciences, Norman; and OU Health Sciences Center Departments of [4]Biostatistics and Epidemiology, [5]Rehabilitation Sciences, and [6]Medicine

Introduction: Skeletal muscle mass (SMM) predicts outcomes in pancreatic cancer and pancreaticoduodenectomy (PD), the only potential cure. Muscle hypertrophy is a leading mechanistic theory for the published benefits of exercise-based prehabilitation ("prehab"). Significant muscle hypertrophy requires 4-8 weeks of exercise in healthy adults, and pancreatic cancer is known to induce muscle loss, yet early evidence suggests that prehab for only 2 weeks before PD may benefit some patients. We hypothesize that these brief exercise programs improve skeletal muscle *quality* more than mass. Phase angle (PhA) is a bioimpedance measure of cell membrane integrity that correlates with muscle quality and predicts better survival in some cancers. We aim to explore PhA and SMM trajectories from a pilot study of high frequency (daily) exercise for 2-3 weeks before PD. To aid interpretation, we will compare results to minimal detectable change (MDC) thresholds we estimate from healthy adults.
Methods: In 45 patients approved for PD (49% female, 71% White) we measured SMM (lbs) and PhA (°) by InBody770 bioimpedance before and after 2-3 weeks of daily prehab, and again after PD. Separately, in 26 healthy adults (58% female, 61% White) we repeated SMM and PhA twice in 1-3 weeks. After estimating test-retest reliability by Intraclass Correlation Coefficient (ICC) we calculated MDC as 1.96 X standard error X √2. In both samples, we compared demographic and body composition variables by cohort or timepoint using Wilcoxon signed rank or linear regression (as appropriate).
Results: ICC = 0.93-0.99. MDC (95% CI) = 0.38-0.66 lbs SMM and 0.07-0.12° PhA. Compared to healthy adults (HA) of similar height (p=0.28), the PD sample was older (65 ± 11 yrs vs 29 ± 7 yrs, p<0.01) and weighed more (178 ± 48 lbs vs 151 ± 24 lbs, p<0.01). After controlling for age & weight, the PD cohort had lower baseline PhA than HA (4.2 ± 1.1 deg vs 5.9 ± 0.8°, p<0.0001), but muscle mass did not differ (64.2 ± 22.5 lbs PD vs 60.2 ± 20 lbs HA, p=0.97). After prehab PhA in the PD cohort improved to 4.5 ± 1.3°

(p<0.001) without a change in SMM (64.6 ± 21.6 lbs, p=0.15). From pre-to-post PD, patients declined in PhA (3.9 ± 1.0 deg) and SMM (63.1 ± 20.0 lbs), p<0.001.
Conclusions: We estimate MDC thresholds as 0.5 lbs SMM and 0.1° PhA in healthy adults. Comparatively and statistically (p<0.001) improvement in PhA (0.3°) exceeded improvement in SMM (0.4 lbs) after brief PD prehab in individuals with active pancreatic cancer. If confirmed in larger studies and using pancreatic cancer-specific MDC estimates, PhA could prove clinically useful to inform exercise prescription by quantifying prehab response. Pre-operatively, PhA and SMM may assist surgeons in prioritizing prehabilitation referrals.
Funding: Presbyterian Health Foundation, Oklahoma TSET, National Cancer Institute Cancer Center Support Grant P30CA225520 to OU Stephenson Cancer Center, American Cancer Society

PERIPHERAL NEUROPATHY PHENOTYPING IN GYNECOLOGIC CANCERS SUGGESTS MOTOR PREDOMINANCE

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Introduction: 70% of patients develop peripheral neuropathy (PN), diagnosed by numb / tingling (NT) toes, with taxane-platinum (t/p) first-line therapy for gynecologic (gyn) cancer. PN leads to chemo dose reduction, doubles fall risk, and can persist for 12 years. PN is viewed as homogeneous and primarily sensory with rare and late motor signs (initially toe weakness, TW), but TW is evaluated by report more often than performance. Clinically, we find TW on manual tests in patients with no reported weakness. In both older adults and patients with diabetic PN, TW contributes to imbalance and is more amenable to rehabilitation than PN symptoms (NT) or sensory loss (SL). Phenotyping t/p-PN by 3 key contributors to imbalance (NT, TW, SL) would inform intervention studies and clinical monitoring and referrals. We aim to estimate the incidence of toe weakness (TW) with t/p exposure, and the temporal relationship to onset of NT symptoms and sensory loss.

Methods: We enrolled women before the 1st of 3-6 t/p cycles for gyn cancer. Before each cycle a research assistant collected 3 validated PN metrics: NT (Functional Assessment of Cancer Therapy Item NTX2), Toe Strength (Manual Muscle Test), Toe Vibration sense (Biothesiometer), and asked about weak feet. We defined onset of NT, TW, SL by the 1st visit of decline from baseline exceeding 1 Likert item, 1 Medical Research Council Scale level, or 4 Volts, respectively. We estimated 4 V using Standard Measurement Error in our healthy adult comparison data. We defined each unique combination of NT, TW, SL as 1 PN phenotype. We used descriptive statistics to estimate frequency [95% confidence interval] of each phenotype, and of NT, TW, SL as 1st symptom detected.

Results: Only 2 (8.7%) of 23 women aged 64.5 ± 11.7 yrs (84% White, 82.5% paclitaxel/ carboplatin, 47.8% diabetes) developed no new or worsening PN. Three PN phenotypes emerged, all with toe weakness: TW/SL/NT in 65.2% [44.9, 81.2%], TW/SL *without* NT in 17.4% [7.0, 37.1%], TW *without* SL or NT in 8.7% [2.4, 26.8%]. Toe weakness was the

1st sign of PN in 47.6% [28.3, 67.6%] of cases. Only 23.8% reported TW at onset, even after observing their own toe tests.
Conclusions: In this small local sample, 91% of gyn patients on t/p developed PN with motor (TW) component. Cases clustered into 3 phenotypes with fall risk implications, including two *without* NT that are not recognized in most clinics or research. In every case of NT, TW co-occurred, and usually came first, suggesting that TW may detect PN earlier. If confirmed in larger samples, these results could change practice. To reduce bias and improve TW sensitivity, we have patented a toe strength quantification device. We are also working with engineering collaborators on a machine-learning algorithm to detect new or worse NT, TW and SL as plantar pressure changes during usual walking.
Funding: Presbyterian Health Foundation, Oklahoma TSET, NCI Cancer Center Support Grant P30CA225520 to OUH Stephenson Cancer Center

LONGITUDINAL APPLICATION OF DATA-DRIVEN MODELLING TO ANALYZE HEEL-TOE PLANTAR PRESSURE TRAJECTORIES IN WOMEN WITH GYNECOLOGIC CANCER DURING NEUROTOXIC CHEMOTHERAPY

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Background: Women with gynecologic (gyn) cancers are at increased risk for falls, and neurotoxic chemotherapy is a known falls risk factor. In each step of typical walking, the heel strikes the ground before plantar pressure quickly transfers to the metatarsals and toes so the foot may "push off" to swing forward. Spatiotemporal patterns at heel (H), metatarsal (MT) and toe (T), particularly if combined in a single model, may identify an individual, and changes from the predominant "baseline" pattern may be clinically useful to identify earliest signals of chemo-induced peripheral neuropathy (CIPN), and perhaps even to distinguish CIPN by motor or sensory phenotype. We aim to explore the feasibility of modeling deviations from a woman's baseline predominant H, MT, and T pressure patterns over successive infusions of neurotoxic chemo.
Methods: TekScan® Strideway™ gait data were used from 15 women (80% White) age 64.5 ± 11.67 years with gyn cancer. A series of 24 steps per foot (right-left) at usual pace was available for each woman before 1st paclitaxel/ carboplatin infusion (baseline, BL) and before 2-5 subsequent cycles. Dynamic Mode Decomposition (DMD)—a data-driven dynamical modeling algorithm— was employed to process time and plantar pressure-varying signals. Time/pressure signals were decomposed into their time decaying harmonics, consisting of dynamic modes and eigenvalues and capturing gait pressure features and their variations exhibited among the steps at H, MT, and T regions. Each foot (right-left) was analyzed separately by patient and visit.
Results: As women accumulated chemotherapy exposure across infusion cycles, the following trends emerged in the dominant DMD modes bilaterally, although asymmetrically: reduction in DMD mode *magnitude* and increase in *oscillation*. Compared to the baseline visit, as women developed CIPN the reduction in magnitude averaged only 2% in the second visit but the reduction was 27% in the fourth visit. Oscillation increased to 61% by the last visit.

Conclusion: From footsteps at usual pace, our DMD approach captured characteristic baseline plantar pressure features at the heel, metatarsals, and toes for women with gyn cancer, and changes that increase over cycles, and are bilateral yet asymmetrical. These are same characteristics are published for CIPN. Now that we have a candidate approach, we will explore associations between changes in DMD modes and clinical labels from patient-reported symptoms and imbalance, and the clinical measures (vibratory sensation and toe weakness) used in phenotyping.

Acknowledgement of Funding: Presbyterian Health Foundation Equipment Grant and College of Allied Health New Investigator Seed Grant, Oklahoma TSET, NCI Cancer Center Support Grant P30CA225520 to OUH Stephenson Cancer Center.

ARTIFICIAL INTELLIGENT FRAMEWORK USING PLANTAR PRESSURES TO DISTINGUISH CLINICAL PERIPHERAL NEUROPATHY PHENOTYPES IN WOMEN'S CANCERS

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Introduction: Gait analysis provides a key barometer to indicate an individual's health status. Since human locomotion generates a repeatable plantar pressure (PP) pattern, changes in the patterns could distinguish the presence of health conditions including peripheral neuropathy in women with gynecologic (gyn) cancers, If sufficiently sophisticated, an automated program may be able to distinguish phenotypes of neuropathy, for example, chemotherapy-induced peripheral neuropathy (CIPN) from diabetic. Previously, we proposed an artificial intelligent (AI) framework for the unique gait baseline using a data-driven dynamical model. Now we aim to show the capability of the technique to distinguish between the causes of its variation. To that end, we investigated the dynamical properties in the PP measured by the Tekscan Strideway pressure mapping device.
Methods: Since the PP patterns show complex non-linear dynamical behaviors, we proposed the data-driven modeling technique called Dynamic Mode Decomposition (DMD) to analyze the measured data in terms of the basis functions in spatiotemporal dimension, characterized by the three dynamical parameters (DP): (1) Frequency (FR) associated with gait cycle temporal structure, (2) Decay Rate (DR) related to the point contact time of foot areas (Heel, Midfoot, Metatarsal, Toes), and (3) Initial Condition (IC) correlated to generate overall PP profile. Isolating a single PP signal from the multiple gait cycles and treating them as a statistical ensemble, we constructed the set of gait features in the given formation parameters. Along with 2D spatial PP's analyzed by the time-invariant basis function, we investigated the relationship between the health conditions and the gait variability in the 1D temporal PP profile in terms of its DP values. After characterizing the PP in each gait cycle, we employed the AI algorithms to the set of parameters to categorize the health conditions of 11 women undergoing neurotoxic chemotherapy for gyn cancer.
Results: Our framework was able to map the pattern variation of gait baseline to gait parameters for 6 of 11 women. We could distinguish CIPN with and without diabetes as well as sensory from motor-predominant neuropathy.

Conclusion: We showed an AI framework for the detection and recognition of the gait variability influenced by CIP patients' health conditions. By differentiating the CIPN from peripheral neuropathy due to other health conditions, the caregivers will be able to perform preemptive prevention to avoid future risks and implement the appropriate treatment in a timely manner, especially for the cancer patient.

Funding: Presbyterian Health Foundation, Oklahoma Tobacco Settlement Endowment Trust, NCI Cancer Center Support Grant P30CA225520 to OU Stephenson Cancer Center.

Cancer Therapeutics

CANCER THERAPEUTICS

Nicholson Tower – Room B

2:30 – 3:35 PM

SESSION II

Cancer Therapeutics

Moderator: Laura Holman

2:35 – 3:05 PM

Association Between Needle Density and Treatment Outcomes in Prostate Cryotherapy

Danielle Digoy
Department of Urology
The University of Oklahoma

3:05 – 3:35 PM

Targeting Solvent-Front Mutants of the Ret Oncokinase

Ujjwol Khatri
Department of Pathology
The University of Oklahoma Health Sciences Center

3:40 – 4:45 PM

SESSION III

Cancer Therapeutics

Moderator: Susanna Ulahannan

3:45 – 4:05 PM

Single-Cell Rna Sequencing Reveals Anti-Tumor Phenotypes in Nk Cells Induced by Both Localized Ablative Immunotherapy (Lait) and Immune Checkpoint Inhibitor (Ici) Therapy

Kaili Lu
Stephenson School of Biomedical Engineering
The University of Oklahoma

4:05 – 4:25 PM

Ultrasound Imaging of PD-L1 Immune Markers by Targeted Microbubbles in A Murine Colon Carcinoma Model

Negar Sedeghipour
Department of Pathology
Electrical and Computer Engineering
The University of Oklahoma

4:25 – 4:45 PM

Treatment-Related Cognitive Impairment in Cancer Patients

Summer Edwards
Department of Biomedical Engineering
The University of Oklahoma

ASSOCIATION BETWEEN NEEDLE DENSITY AND TREATMENT OUTCOMES IN PROSTATE CRYOTHERAPY

Danielle Digoy, Alexandria Childs, Michael Cookson, Kelly Stratton
Department of Urology, University of Oklahoma

Background: Ablative treatments such as prostate cryotherapy are limited by anatomical factors including treatment volume. The number of needles necessary for treatment of varying prostate sizes (needle density) has not been standardized. Our aim in this study is to evaluate the impact of needle density to identify patients receiving inadequate treatment.
Methods: We retrospectively reviewed our institutional database of patients undergoing prostate cryotherapy. Patients were excluded if they were lost to follow up or received previous treatment for prostate cancer. Needle density was calculated by dividing the number of needles by the prostate grams measured by MRI. The mean value was compared with treatment failure through a chi-squared test. Treatment failure was defined as tumor recurrence on post-treatment biopsy.
Results: Of 91 patients, 62 met the inclusion criteria for this study. Tumor recurrence was found in 17 of 62 (27%) patients. There was a higher average prostate size of 47 grams in patients experiencing recurrence compared to the overall average of 40 grams. Of the 17 patients experiencing recurrence, 13 (76%) received treatment below the mean needle density of 0.12 (p-value of 0.039). The needle density threshold of 0.12, or >1.2 needles per 10 grams of prostate, was used to generate Table 1 based on prostate size.
Limitations: A limiting factor of this study is the sample size. Ideally, we would like to examine the effects of needle density on a larger quantity of patients. Additionally, a larger study which can standardize cancer grade group may better evaluate treatment needs. We also accept that larger tumors may exhibit recurrence regardless of needle density. Further studies are necessary to fully standardize appropriate needles.
Conclusion: This study identified the association of needle density treatment outcomes in prostate cryotherapy. A needle density below 0.12 needles/gram was associated with cancer recurrence on post-treatment biopsy. Based on our findings, we propose a table standardizing the needles necessary for treatment based on measured prostate volume.

Table 1. Prostate Size with Number of Needles Necessary for Appropriate Needle Density

Prostate Size (grams)	**Needles Needed**
10	2
20	3
30	4
40	5
50	6
60	6+

TARGETING SOLVENT-FRONT MUTANTS OF THE RET ONCOKINASE

Ujjwol Khatri[1], Xueqing Hu[1], Tao Shen[1], Xuan Liu[1], Herman Sintim[2], and Jie Wu[1]
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Rearranged during transfection (RET) is a protein tyrosine kinase that is aberrantly activated by gene fusions or mutations in many types of human cancer including thyroid cancer and non-small cell lung cancer (NSCLC). Selpercatinib (LOXO-292) and pralsetinib (BLU-667) are FDA approved RET-selective tyrosine kinase inhibitors (TKIs) for treating RET-altered cancers. In clinical studies, both inhibitors are effective on RET(V804M/L) gatekeeper mutants but are subject to resistance from acquired RET(G810C/R/S) mutations located at the solvent front of the ATP binding pocket. The objective of this study is to extend the sensitivity profile of RET solvent-front mutants and identify new RET TKIs capable of inhibiting these mutants based on hypothesis that certain nicotinamide analogs of TKIs are potent inhibitors of RET solvent-front mutants. In addition to previously identified RET(G180C/S/R/A) mutations and V804L/M mutations, we constructed all six possible nonsynonymous single nucleotide substitutions of G810 mutations in the KIF5B-RET fusion oncogene. Established RET kinase-dependent BaF3 cells expressing these mutants were profiled for their sensitivities to selpercatinib, pralsetinib, and candidates of nicotinamide-based RET TKIs identified from our cell-based screening. HSN608 was further selected for testing in xenograft tumors. We identified G810D as a novel selpercatinib/pralsetinib-resistant mutant. Interestingly, the acquired G810V mutant previously reported in a selpercatinib-treated NSCLC patient was found to be sensitive to selpercatinib and pralsetinib. Seven nicotinamide-based RET TKIs that we analyzed were able to inhibit all six G810 mutants and V804M/L mutants with low nanomolar IC_{50}s. In animal xenograft tumors, HSN608 induced G180C tumor regression at a tolerated dose. Thus, we have established the sensitivity profiles of selpercatinib and pralsetinib on RET G810 mutants. We have also identified potent compounds with excellent aqueous solubility for inhibiting gatekeeper mutant as well as all possible mutations at the solvent-front residue of the oncogenic RET kinase.

This study was supported by the National Institutes of Health grants R01CA273168, R41CA250707, P30CA023168, P20GM103639; a PHF SEED grant, OCAST grant HR19-026, and the Oklahoma Tobacco Settlement Endowment Trust either to JW or to the Stephenson Cancer Center.

SINGLE-CELL RNA SEQUENCING REVEALS ANTI-TUMOR PHENOTYPES IN NK CELLS INDUCED BY BOTH LOCALIZED ABLATIVE IMMUNOTHERAPY (LAIT) AND IMMUNE CHECKPOINT INHIBITOR (ICI) THERAPY

Kaili Liu[1], Negar Sadeghipour[1], Ashley R. Hoover[1], Trisha I. Valero[1], Coline Furrer[1], Jacob Adams[1], Abdul Rafeh Naqash[2], and Wei R. Chen[1]*

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Natural killer (NK) cells provide protective anti-cancer immunity. However, the cancer therapy induced activation gene signatures and pathways in NK cells remain unclear. We applied a novel localized ablative immunotherapy (LAIT) by synergizing photothermal therapy (PTT) with intra-tumor delivering of the immunostimulant N-dihydrogalactochitosan (GC), to treat breast cancer using a mammary tumor virus-polyoma middle tumor-antigen (MMTV-PyMT) mouse model. We performed single-cell RNA sequencing (scRNAseq) analysis to unveil the cellular heterogeneity and compare the transcriptional alterations induced by PTT, GC, and LAIT in NK cells within the tumor microenvironment (TME). ScRNAseq showed that NK subtypes, including cycling, activated, interferon-stimulated, and cytotoxic NK cells. Trajectory analysis revealed a route toward activation and cytotoxicity following pseudotime progression. Both GC and LAIT elevated gene expression associated with NK cell activation, cytolytic effectors, activating receptors, IFN pathway components, and cytokines/chemokines in NK subtypes. Single-cell transcriptomics analysis using immune checkpoint inhibitor (ICI)-treated animal and human samples revealed that ICI-induced NK activation and cytotoxicity across several cancer types. Furthermore, ICI-induced NK gene signatures were also induced by LAIT treatment. We also discovered that several types of cancer patients had significantly longer overall survival when they had higher expression of genes in NK cells that were also specifically upregulated by LAIT. Our findings show for the first time that LAIT activates cytotoxicity in NK cells and the upregulated genes positively correlate with beneficial clinical outcomes for cancer patients. More importantly, our results further establish the correlation between the effects of LAIT and ICI on NK cells, hence expanding our understanding of mechanism of LAIT in remodeling TME and shedding light on the potentials of NK cell activation and anti-tumor cytotoxic functions in clinical applications.

Keywords: Single-cell RNA sequencing, NK cell activation, localized ablative immunotherapy, immune checkpoint inhibitor therapy, N-dihydrogalactochitosan, breast cancer

ULTRASOUND IMAGING OF PD-L1 IMMUNE MARKERS BY TARGETED MICROBUBBLES IN A MURINE COLON CARCINOMA MODEL

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Background. Cancer patients may benefit from immune therapies, including immune checkpoint inhibitors (ICIs). These agents block the immune suppressive markers that are highly expressed in tumors. As a result of the treatment, immune cells, including T-cells can infiltrate tissue and kill cancer cells. ICI treatment is very successful in a subset of cancer patients. However, many patients do not respond to ICI or become resistant after the initial response. ICI treatment is particularly challenging in solid tumors where the expression of immunosuppressive molecules on the endothelial cells inhibits the immune cells from trafficking to the tissue, known as endothelial cell anergy. In this study, we imaged the expression of one of these immunosuppressive markers called programmed death-ligand 1 (PD-L1) on the endothelial cells of colon carcinoma using targeted contrast-enhanced ultrasound.

Methods. Female BALB/c mice aged 6-8 weeks were used in this study. All animal procedures were approved by administrative panel on laboratory animal care at Stanford University. To image the expression of PD-L1 markers in mice, we used target-ready streptavidin conjugated lipid shelled microbubbles. We implanted 3×10^6 CT26 cells (murine colon carcinoma cell line) into the lower flank of Balb/c mice. The tumors were allowed to grow and reach 5 mm/diameter before imaging. On the day of imaging, isotype (MB_{iso}) and PD-L1-targeted (MB_{PDL1}) microbubbles were prepared based on the manufacturer's protocol. For imaging procedures mice were anesthetized with 1-3% isoflurane. Ultrasound imaging was performed with a preclinical Vevo2100 system with M250 transducer by placing a catheter in the tail vein. A total of 50 µl of microbubbles (30e6 bubbles/mouse) diluted in 150 µl of saline were injected. Perfusion signals as well as differential targeted enhancement values (dTE) were quantified. Destructive signals were applied, dTE values were recorded. The experiment was repeated in mice receiving different immunomodulator agents to quantify the level of PD-L1 under those

conditions. We also showed the expression of PD-L1 in different cancer cell lines and endothelial cells in vitro using FACS and Western Blotting analysis.
Results. Upon incubation of different cell lines with IFN-γ, PD-L1 expression on the endothelial cells increases about 10-fold which was comparable to cancer cell lines. In vivo, we observed specific binding of $MB_{PD\text{-}L1}$ to the targets. The elevated dTE signal in animals imaged with PD-L1 MBs was (~13.27 a.u, n = 4) vs. isotype (~5.42 a.u., n =4). In a follow-up study, we blocked the tumors with anti-PD-L1 antibody. The post-blocking signal dropped by 2 fold compared to the baseline signal showing that our imaging method can quantify changes in PD-L1 expression.
Conclusion. We successfully demonstrate that PD-L1 can be targeted using ultrasound molecular imaging *in vivo*; this would find application in screening patients who may respond to immunotherapy at bedside.

TREATMENT-RELATED COGNITIVE IMPAIRMENT AND NEUROVASCULAR COUPLING IN CANCER PATIENTS

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Introduction: Functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG) are two modes of brain imaging used to detect neurovascular coupling (NVC). NVC refers to the connection between change in blood flow to the brain and neural activity response, which could be altered or affected by various factors including but are not limited to aging, disease, drug abuse, and medical treatment. The goal of the current study is to determine the effects of chemotherapy on NVC in ovarian cancer patients receiving chemotherapy treatment, through measuring and comparing fNIRS and EEG responses pre and post treatment.

Materials and Methods: This is a prospective single-institution pilot study of 14 women diagnosed with advanced stage ovarian cancer. Thus far, fNIRS and EEG recordings have been collected in three patients before and after receiving cancer treatment. Each subject completed 5 recording sessions including 2 resting state, 2 motor calibration tasks, and 1 attention network task (ANT), during which simultaneous fNIRS and EEG were recorded. Motor tasks included 7 blocks of fist clenching for 20 seconds at 1Hz with 30 seconds of resting between. Resting states included 6 minutes of pure rest with the subject only directed to look at a cross symbol on a computer screen. The ANT included various symbols that appeared on the computer screen with specified participant responses. A plus sign, dot, and sometimes a star appeared on the screen with arrows pointing in different directions around them. Participants were asked to determine which way the arrow directly above or below the plus sign was pointing and press the designated key for arrow direction. Response time and accuracy were recorded to determine cognitive impairment.

Results and Discussion: Currently, pre and post treatment data have been collected in 3 out of a planned 14 patients. Our results have shown consistent increases in oxygenated hemoglobin signals with concomitant decreases in deoxygenated hemoglobin signals during motor tasks, which is consistent with the neurovascular coupling process. Further analysis will include the assessment of attention performance, in comparison with differential NVC responses before and after treatment. It is hypothesized that chemotherapy will induce treatment-related cognitive impairment, however, the magnitude of impairment is to be determined.

Conclusion: Our study has demonstrated the feasibility of measuring neurovascular coupling in cancer patients. Through continuing data collection, the project is expected to yield new knowledge on the cognitive and cerebrovascular effects of chemotherapy in ovarian cancer patients, which can potentially lead to further advances in brain protection during treatment.

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NOVEL MODEL FOR STUDYING THE PROGRESSION OF METASTATIC COLORECTAL CANCER WITH STEM CELL ORIGINS

Saad Ahmed[1], James Griffith[1], Shaoxuan Guo[1], Tae-Dong Kim[1], Megan Lerner[1], Lacey McNally[1,2], Katherine Morris[1,2], and William Berry[1,2].

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Colorectal cancer (CRC) is the second leading cancer related cause of death worldwide, responsible for nearly 2 million deaths annually, most commonly due to complications from metastasis. A genetic mouse model that faithfully reproduces human metastatic CRC (mCRC) is therefore critically important to support pre-clinical research in the field. Recently, a novel inducible genetically engineered mouse model in an immune competent B6 background was developed that metastasizes to the lung, liver, and peritoneum, recapitulating what is seen in CRC patients. This model uses the Lgr5 (L) promoter to drive tamoxifen inducible Cre recombinase with the following conditional alleles: Apc (A), mutant Kras G12D (K), Tgfbr2 (T), and p53 (P) (LAKTP). The Batlle lab described this model as developing mCRC derived from intestinal Lgr5 positive stem cells upon tamoxifen induction. However, after establishing the model in our center, we found mice developing tumors in the absence of tamoxifen induction. Since the original model lacked the ability to monitor tumor development and progression *in vivo,* in real time, we created an LAKTP based mouse model that would allow for monitoring of tumor growth over time, enabling us to determine the frequency and time course of tumor development. Lastly, we added conditional Nuclear Tagging and Translating Ribosome Affinity Purification (NuTRAP) allele, which allows for the isolation of ribosomes and nuclei only from Lgr5 positive tumor cells.

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Optical Coherence Tomography Angiography Monitors the Characteristics of Vascular Diameter Distribution and Tortuosity in Aging Mouse Brain

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Quantifying vascular changes is important in medical research to assess the effects of a drug or treatment on the subject. This paper introduces image processing methods to quantify blood vessel diameter distribution and vascular tortuosity, to be employed in the analysis of mouse brain microvasculature with aging as a metric to compare the effects on cerebral microvasculature of chemotherapy. In this study, blood vessel images were obtained with Optical Coherence Tomography Angiography (OCTA). Blood vessel diameter distribution was computed using Zhang-Suen thinning to generate vessel centerlines; distance transform was applied along the centerlines to obtain vessel diameters, which were plotted as a probability distribution function. To quantify vascular tortuosity, the program segmented and smoothed the imaged vessels, which were processed using a Vessel Tortuosity Index (VTI) algorithm to obtain the mean tortuosity index value. Our results found that a significant difference in vascular diameter distribution existed between brain microvasculature with young and old mice. The tortuosity of blood vessels with different sizes in old mouse brain vasculature was significantly different from the young mice. This study demonstrated that these novel quantitative blood vessels parameters hold the promise to monitor the age-related change of the microvasculature in the mouse brain in order to draw correlation with the effects of cancer therapeutics.

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FINANCIAL HARDSHIP SCREENING AMONG NATIVE AMERICAN PATIENTS WITH CANCER: A QUALITATIVE ANALYSIS

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Cancer-related financial hardship is an increasingly recognized problem for patients, families and caregivers. Many Native American patients, including persons of American Indian or Alaska Native descent, may be at increased risk for cancer-related financial hardship due to highly prevalent factors, such as low income, medical comorbidity, and lack of private health insurance coverage. We conducted key informant interviews with eleven Native American patients with cancer and clinical staff at a single cancer center in Oklahoma. Patient interviews included questions about current financial hardship, experiences in discussing financial hardship with the cancer care and primary care team, and acceptability of completing a financial hardship screening tool at the cancer center. Clinician interviews focused on confidence, comfort, and experience in discussing financial hardship with patients. Recorded interviews were transcribed and thematically analyzed using MAXQDA® software.

Patients expressed many financial challenges to receiving cancer care. The most frequently stated challenges included transportation, lodging during treatment, food insecurity, and utility expenses. Patients were willing to complete a financial hardship screening tool, but indicated this tool should be short and not overly intrusive of the patient's finances. Clinical staff described discomfort in discussing financial hardship with patients, primarily due to a lack of training and knowledge about resources to support patients. There were also differing perspectives on who should be responsible for addressing financial hardship and timing of such screening.

We identified facilitators and barriers at both the patient and clinician levels to complete a financial hardship screening tool. These preliminary findings suggest that cancer centers need to develop clear organizational structures and processes for financial hardship to be addressed effectively. We are currently implementing a

screening tool in a pilot study and conducting additional interviews among patients and clinical staff to identify methods to address financial hardship among Native American cancer patients. Findings from the pilot intervention will also be presented.

This pilot study was funded by the National Cancer Institute Grant Number P30CA225520-03S6 (National Cancer Institute) and by the Stephenson Cancer Center.

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PERCEIVED DISCRIMINATION IS RELATED TO DAILY CANCER RISK BEHAVIORS

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Introduction: Discrimination, the unjustified or prejudicial treatment of people and groups based on qualities such as race, age, gender, or sexual orientation, can harm individual well-being. Prior research suggests daily discrimination events are associated with higher stress and depressive symptoms, which may lead to greater cancer risk behaviors, such as increased alcohol use, drug use, smoking, and lack of sleep. The purpose of this study was to examine relationships between discrimination events and next-day cancer risk behaviors.

Methods: Eligible participants (N = 434) received 2-4 prompted daily Ecological Momentary Assessments (EMAs) on their personal smartphones for 28 days. The EMAs were brief 1-2-minute surveys mostly assessing daily health behaviors and affect. Measures included items that assessed daily marijuana use, alcohol use, cigarettes smoked, sleep hours, sleep quality, physical activity levels, fruit and vegetable consumption, and soda intake. Previous-day perceived discrimination was measured each morning. Participants were asked, “Do you believe you experienced discrimination yesterday?” with Likert scale answer options, ranging from “No” to “Yes, absolutely sure.”

Results: The sample was 71.7% White, 77.0% Female, and 48.3 years old (SD_{age} = 12.3). Multilevel time lag analyses were conducted with 28 days of EMA data. Perceived discrimination (Day 1) had a significant positive effect on several next-day health behaviors (Day 2). Specifically, previous day discrimination increased the likelihood of next day smoking (Est = 1.90, t = 1.78, $p < 0.1$), cannabis use (Est = 0.07, t = 2.96, $p < 0.05$), soda intake (Est = -0.003, t = -1.91, $p < 0.05$), and vigorous physical activity (Est = 0.05, t = 0.58, $p < 0.05$). Perceived discrimination also had a significant negative effect on sleep quality (Est = -.33, t = -2.41, $p < 0.05$).

Discussion: Study findings indicated that perceived discrimination events among a nationwide sample of adults may increase engagement in next-day cancer risk behaviors (i.e., cigarette smoking, cannabis use, and sugared drink consumption). Unexpectedly, discrimination events were related to an increase in next day vigorous physical activity. Future research should seek to elucidate mechanisms linking observed relationships between discrimination and cancer risk behaviors.
Funding: This study was supported by the Oklahoma Tobacco Settlement Endowment Trust (grant number R21-02) and used the mobile health shared resource of the Stephenson Cancer Center via an NCI Cancer Center Support Grant (grant number P30CA225520).

TRANSCRIPTOMIC ANALYSIS PROVIDES INSIGHT INTO THE MECHANISM OF IKKB-MEDIATED SUPPRESSION OF HPV18E6-INDUCED CELLULAR ABNORMALITIES

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High-risk Human Papillomaviruses (HPV) 16 and 18 are responsible for more than 70% of cervical cancers and majority of other HPV-associated cancers world-wide. Current treatments for these cancers have limited efficacy, which in turn has resulted in disease recurrence and poor survival rates in advanced disease stages. Hence, there is a significant need for development of novel molecularly-targeted therapeutics. This can only be achieved through improved understanding of disease mechanism. Recently, we developed a *Drosophila* model of HPV18E6 plus human E3 ubiquitin ligase (hUBE3A) and demonstrated that the E6-induced cellular abnormalities are conserved between humans and flies. Subsequently, we demonstrated that reduced level and activity of IKKβ, a regulator of NF-κB, suppresses the cellular abnormalities induced by E6 oncoprotein and that the interaction of IKKβ and E6 is conserved in human cells. In this study, we performed transcriptomic analysis to identify differentially expressed genes that play a role in IKKβ-mediated suppression of E6-induced defects. Transcriptome analysis identified 215 genes whose expression were altered due to reduced levels of IKKβ. Out of these 215 genes 151 genes showed annotations. These analyses were followed by functional genetic interaction screen using RNAi, overexpression, and mutant fly strains for identified genes. The screen identified several genes including genes involved in Hippo and Toll pathways as well as junctional complexes whose downregulation or upregulation resulted in alterations of E6-induced defects. Subsequently, RT-PCR analysis was performed for validation of altered gene expression level for a few representative genes. Our results indicate an involvement for Hippo and Toll pathways in IKKβ-mediated suppression of E6+hUBE3A-induced cellular

abnormalities. Therefore, this study enhances our understanding of the mechanisms underlying HPV-induced cancer and can potentially lead to identification of novel drug targets for cancers associated with HPV.

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DEVELOPMENT OF NEW OXYSTEROL-BINDING PROTEIN (OSBP)-TARGETING ANTICANCER COMPOUNDS

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Recently, oxysterol-binding proteins (OSBPs) have been demonstrated to be potentially druggable precision anticancer and broad-spectrum antiviral targets. OSBP was shown to regulate mTORC1 activity, which would both limit cancer proliferation and viral protein translation. Additionally, OSBP-related protein 4 (ORP4), which is closely related in its sequence to OSBP, is not required for viral proliferation but is selectively expressed in many human cancers, where ORP4 has been shown to drive cancer cell proliferation. The natural product compound OSW-1, isolated from the plant *Ornithogalum saundersiae*, is a potent anticancer and antiviral agent through targeting ORP4 and OSBP, and therefore a starting point for drug targeting of these proteins. The goal of this research project is to produce OSW-1-related compounds for potential drug development, including selective ORP4-targeting anticancer compounds. Currently there are no reported protein structures of ORP4 or OSBP. To develop an OSW-1 SAR, a library of OSW-1-related compounds will be produced for *in vitro* ORP4 and OSBP binding studies and biological evaluation. In this project, two approaches for producing OSW-1-related compounds for SAR studies will be reported. The first approach is done via isolation of these OSW-1-related compounds from the natural plant source, including a new compound that has not been previously reported. The second approach is to modify the existing OSW-1 structure, including through the synthesis of OSW-1 Fluorescent and PROTAC analogs. Determining the binding affinity to ORP4 and OSBP and the biological activity of these related OSW-1 compounds will provide further understanding of OSW-1 SAR and progressively guide the development of new ORP4-targeting compounds for pre-clinical drug development as novel anticancer drugs.

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HPV SELF-COLLECTION: WHAT ARE WE WAITING FOR? EXPLORATION OF ATTITUDES FROM FRONTLINE HEALTHCARE PROVIDERS

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Objective: Polymerase chain reaction (PCR)-based human papilloma virus (HPV) self-collection for cervical cancer screening is well established. It is utilized worldwide, accepted by patients, is cost-effective, has comparable sensitivity to provider-collected samples, and increases screening rates, however clinical practice in the United States has not shifted to include HPV self-collection. This study sought to examine provider knowledge and attitudes to better understand why HPV self-collection is not being utilized.

Methods: We conducted an observational, qualitative study. Data were collected with semi-structured focus groups and individual interviews with Oregon health care providers. We continued conducting focus groups and interviews until data saturation was achieved. A grounded theory method was used for analysis, a cyclical process of coding data, memo-writing, and theoretical sampling to the point of saturation.

Results: Eighteen health care providers participated in the focus group and interviews. They represented 14 of 36 counties across Oregon and 50% were physicians, 33% were nurse practitioners, and 94% worked within family medicine. All providers performed cervical cancer screening according to current American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines. Five overarching themes emerged: provider concerns, clinical and provider barriers, patient perspective and barriers, process-based themes, and barriers to cervical cancer screening. Nearly all providers stated they will offer HPV self-collection to most of their patients once available.

Conclusion: While providers identified concerns and barriers for initiating HPV self-collection, there was a strong desire to implement HPV self-collection and assumed acceptance within their patient populations. Providers indicated the need for HPV self-collection to be incorporated into national screening guidelines along with best practices on how to successfully implement this modality to further increase cervical cancer screening rates.

INHIBITING OVARIAN CANCER PROLIFERATION THROUGH TARGETING OF OXYSTEROL-BINDING PROTEINS AND INTRACELLULAR LIPID TRANSPORT

Richard Bui, Jorge L Berrios Rivera, Susan L Nimmo, Anthony W. G. Burgett

Ovarian cancer has a poor prognosis due to diagnosis commonly occurring at the later stages of the disease. During this progression, cancer cells are shed from tumor mass as cells and spheroids, the latter being more resistant to standard-of-care (SOC) chemotherapies. These spheroids metastasize throughout the peritoneal cavity, rather than hematogenous or lymphatic route. Lacking vasculature during proliferation and spread, they exist in an oxygen, cholesterol, and other nutrient lacking environment, at least compared to blood serum. Suggestively, serum cholesterol and LDL levels are reported to be associated with aggressiveness and poor survival outcomes of the disease, indicating a possible link between cholesterol access and ovarian cancer spheroid pathology. as the principal mechanism for disease progression and the development of chemoresistance, novel compounds that can effectively target the multicellular cancer spheroids would be promising new routes to therapeutics. Additionally, novel treatments that selectively targeted the possible cholesterol and nutrient poor state of the ovarian cancer spheroids could be cancer-specific, precision treatments. We have demonstrated that a compound that targets oxysterol-binding protein (OSBP) and OSBP-related protein 4 (ORP4) has nanomolar anticancer activity against *in vitro* ovarian cancer spheroids, far outperforming standard of care (SOC) drugs paclitaxel and cisplatin. OSBP and ORP4 are non-enzymatic lipid binding and transporting proteins. OSBP regulates the correct movement of cholesterol in the cell; the cellular function of ORP4 is unclear, but ORP4 is highly and selective expressed in cancer tissue, especially ovarian cancer tissue. Our hypothesis is that ovarian cancer spheroids, as non-vascularized multicellular structures, are highly sensitive to perturbations in cholesterol transport and usage, and that OSBP/ORP4 targeting compounds exploits this sensitivity to kill ovarian cancer spheroid cells. In support of this hypothesis, I have shown that both lipid depletion in culture media and statin-drug blocking of cholesterol biosynthesis highly potentiates the anticancer activity of the OSBP/ORP4 targeting compound, but not, SOC compounds paclitaxel and cisplatin. Our results support a model of potentially developing OSBP-specific and ORP4-specific compounds to further uncover the mechanisms of the two targets.

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IL-23 KNOCKDOWN PROFOUNDLY SUPPRESSES INTESTINAL TUMORIGENESIS IN APC^{MIN} MICE

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Colorectal cancer (CRC) is the 3rd most common cancer in the United States with an estimated 149,500 new cases and 52,980 deaths in 2021. Studies have shown that Western-style diet-induced obesity may promote CRC by modulating gut inflammatory mediators. Our results suggest a significant increase in IL-23 levels ($p<0.0001$) in plasma from obese human subjects (n=15/arm; BMI>30). Further, IL-23 over expression was observed in colonic tumors (CT) from human and rodent models that was strongly supported by, and highly correlated with, the TCGA gene expression & disease-free survival data. These findings suggested IL-23 as a possible important link between obesity and colon tumorigenesis. The present study was designed to understand the role of IL-23 in colorectal carcinogenesis by using genetic knockout (KO) approach. For this study, $Apc^{min/+}$ and IL-23 KO mice were crossbred to generate $Apc^{min/+}$ mice with IL-23 in heterozygous or KO conditions. To determine the effect of IL-23 on intestinal tumorigenesis, six-week-old $Apc^{min/+}$ mice (N≥15/gender) were grouped by IL-23 genotype i.e., normal (+/+), heterozygous (+/-) and KO (-/-) conditions, then maintained under standard conditions. At 20 weeks of age, all mice were euthanized and intestines were evaluated and compared for tumors incidence and multiplicity. Genetic ablation of IL-23 led to significant suppression of large and small intestinal tumors of $APC^{min/+}$ mice in both genders. Male and female IL-$23^{+/-}$ $Apc^{min/+}$ mice had 77% ($p<0.0001$) and 90% ($p<0.002$) inhibition of CTs, respectively. Interestingly, IL-23 KO led to further suppression in male mice (96% inhibition in male; $p<0.0001$ and 90% in females; $p<0.0001$). While IL-$23^{+/+}$ $Apc^{min/+}$ mice was 91% and 52% CT incidence in the male and female mice, respectively. CT incidence was suppressed by 72% (male, $p<0.0001$) & 88% (female, $p<0.005$) in the IL-$23^{+/-}$ mice, with further suppression to 95% (male, $p<0.0001$) & 89% (female, $p<0.0025$) inhibition in IL-23 KO mice. The strong suppressive effect of IL-23 knockdown was also observed on the small intestinal polyps (SIP) multiplicity. There was a 54% ($p<0.0001$) and 58% ($p<0.0001$) reduction in SIP number in IL$23^{+/-}$ and IL$23^{-/-}$ male $Apc^{min/+}$ mice, compared to the IL-$23^{+/+}$ control mice. In female, 55-59% ($p<0.0001$) less SIP were observed with IL-23 ablation compared to control. $Apc^{min/+}$ with IL-23 KO showed significant reduction in circulating proinflammatory cytokine and chemokines (Ex: IL-1, IL-10, IL-17, IL-23, CCL-2, CCL-3, CCL-5, TNFa, IFNg) levels compared to IL-23 WT mice. These results clearly demonstrate the colon tumor-promoting role of IL-23 and strengthens our hypothesis to

explore this target for CRC prevention in high-risk obese individuals. (Supported in part by P30 CA225520 and Kerley-Cade Endowed Chair)

EXAMINING PUFFING TOPOGRAPHY AMONG POD AND MOD BASED ELECTRONIC CIGARETTE USERS

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Background: Electronic cigarettes (e-cigarettes) come in a variety of styles with unique functions, making it difficult to standardize, test and regulate. Understanding exposures and potential health effects of e-cigarettes is complex. E-cigarettes deliver an aerosol to users by heating a coil and liquid that generally consists of propylene glycol, vegetable glycerin, artificial flavorings, and varying concentrations of nicotine. Users puffing behavior affects function of e-cigarette devices and composition of their aerosol. Users with different topographies are likely exposed to different amounts of any harmful components. For regulatory purposes and the protection of public health, it is essential to assess user puffing behavior, nicotine intake, and patterns of usage across different device models. It is essential to understand the topography and characteristics of e-cigarettes use, which can be helpful to establish standardized protocols for the safety of users.

Objective: The aim of this study was to examine puffing behavior and topography among POD and MOD e-cigarette users.

Methods: Participants 21-35 years old were recruited through mass e-mail, flyers, Facebook and twitter ads. Based on the online survey answers, participants were classified as POD or MOD users based on the device and nicotine (free or salt) in e-liquid. Participants were asked to vape for 2h and the topography data was recorded using an e-Top device. Saliva and blood samples were collected before and after the vaping session. Study was conducted between March 2021 to January 2023. Data were analyzed using Student's t-test.

Results: A total of 53 two-hour vaping sessions were analyzed from 23 POD and 9 MOD users. Male to female ratio was approximately 1:2 in both groups of users. POD users were significantly younger (27.5 ± 4.7 years) than MOD users (31.2 ± 3.7 years). The puff volume, flow rate, and total inhaled volume were significantly higher in MOD then POD users. Average puff duration was similar among both groups of users. However, based on puff duration 2 distinct vaping patterns were identified within each group, with a small group of POD and MOD users having a median puff duration of 5 secs. After, the 2h vaping session plasma nicotine and saliva cotinine were higher in the POD group when compare to MOD users.

Conclusion: In our small series, MOD users are older than POD users. POD users had smaller puff volume, flow rate, and total inhaled volume than MOD users, suggesting that overall, they were

exposed to lower amounts of chemicals. However, they attained higher plasma nicotine and salivary cotinine than MOD users. This most probably reflects the fact that in our series, all POD e-liquids contained nicotine salt. These results establish critical knowledge on distinct vaping topography essential to understand chemical exposure and guide evidence-based regulation for e-cigarettes use.

Grant support: This work was supported by NIH/NCI (R01CA242168, Queimado) and the TSET. Dr. Queimado holds a PHF Endowed Chair in Otorhinolaryngology.

COVID-19 IMPACT ON ACCESS TO HEALTHCARE AMONG AMERICAN INDIAN INDIVIDUALS DIAGNOSED WITH OR TREATED FOR CANCER

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Background: The COVID-19 pandemic resulted in unprecedented disruptions in necessary services including healthcare services. Early detection and treatment of cancer improves cancer survival. American Indian/Alaska Native (AI/AN) people have a higher prevalence of cancer and experience access to healthcare issues more often than other groups. This study aims to evaluate if AI/AN individuals had difficulty obtaining healthcare services during the pandemic. Particularly, we aim to assess if AI/AN individuals diagnosed with or treated for cancer had difficulties accessing healthcare during the COVID-19 pandemic.

Methods: We conducted a population-based survey of AI/AN people residing in the Cherokee Nation Reservation. Surveys were mailed to individuals in census tracts with a high percentage of AI/AN residents using Marketing Systems Group (MSG), which has access to United States Postal Service (USPS) addresses. Survey questions related to events and experiences during the COVID-19 pandemic, including access to healthcare. The survey also included questions about participant's overall general health and previous diagnoses of chronic diseases including cancer. Participants included 343 AI/AN adults living within the Cherokee Nation reservation. We present descriptive statistics (count and percentage) to summarize the data, examining the sample overall and as stratified by demographic and health variables. For all variables, we conducted group comparisons using chi-square test or Fisher's exact test for cell sizes < 5 when indicated. Finally, we conducted multivariate logistic regression analyses to assess associations between recent cancer diagnosis or treatment and access to healthcare issues.

Results: Overall, about 21% (N=68) of respondents reported that getting healthcare for themselves or their family had been challenging during the previous 6 months. Also, about 2% (N=7) reported having a cancer diagnosis and/or cancer treatments within the past 12 months. More than 57% of AI/AN individuals who reported cancer diagnosis/treatment also reported access to healthcare challenges for themselves or family members. Comparatively, only 20% of individuals without a cancer diagnosis or

cancer treatment reported having difficulties (p = 0.04). When controlling for age, insurance status, loss of income, and transportation issues, individuals diagnosed or treated for cancer had greater odds of reporting access to healthcare challenges when compared to those without a cancer diagnosis or cancer treatment (aOR: 7.87, 95%CI 1.33-46.41).
Conclusion: This study indicated that COVID-19 might have negatively affected access to healthcare among AI/AN individuals diagnosed with or treated for cancer. Further studies should explore this potential impact, as early diagnosis and treatment are vital in long-term cancer survivorship. It is important to understand this impact among AI/AN populations as AI/AN people experience higher rates of cancer.

IMPACT OF PTCL-NOS PRIMARY DISEASE SITE ON SURVIVAL

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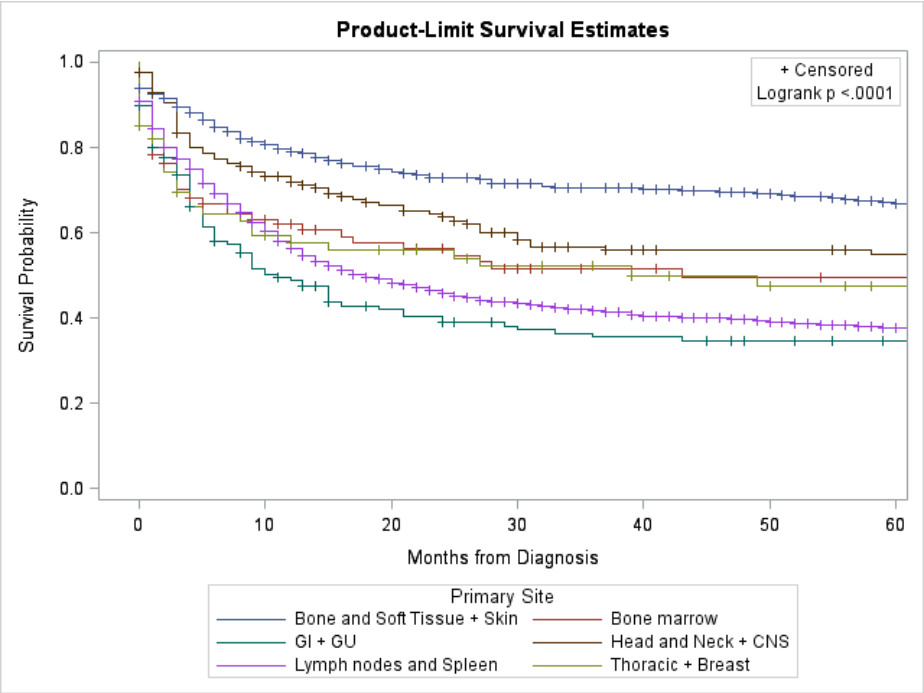
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a rare group of mature T cell neoplasms associated with poor outcomes. It can originate in lymphoid or non-lymphoid tissues including those in the genitourinary system, gastrointestinal tract, bone, skin, soft tissue, lymphatics, reticuloendothelial system, and central nervous system. Previous studies have identified clinical and biochemical characteristics of PTCL-NOS that may influence a patient's prognosis, but little is known about the role that primary disease site plays in patient survival. The goal of this study was to identify the impact of PTCL-NOS primary organ site on survival using a national patient database. The National Cancer Institute SEER database was used to collect data concerning demographics, primary disease site, lymph node involvement, Ann Arbor staging, and survival for patients with PTCL-NOS. Primary disease sites were grouped into seven categories: lymph nodes/spleen, bone marrow, head/neck/central nervous system, thoracic/breast, gastrointestinal/genitourinary, bone/soft tissue/skin, and unknown primary site. Data was extracted, coded, and analyzed using summary statistics, Cox-Proportional Hazards Models, and the Kaplan-Meier method. Univariate and multivariate analysis were utilized for adjusted survival analyses.
Patient data was identified and extracted for a total of 3095 patients and included in the final analysis. A majority of patients were male (60%) and identified as non-Hispanic white (68%) with a median age of 61 years. Stage IV disease was the most common (32%) followed by stage I disease (21%). The most common primary disease site was lymph nodes and spleen (67.2%) followed by bone, soft tissue, and skin (16.2%). Median overall survival for all disease sites was 27 months [95% CI, (24-34)]. Median overall survival was greatest for head, neck, and CNS disease sites (95 months) and lowest for gastrointestinal and genitourinary disease sites (11 months).
PTCL-NOS of the gastrointestinal and genitourinary systems was associated with worse overall survival [HR=1.92 (1.46-2.52); p <0.001] and lymphoma-specific survival [HR=1.76 (1.28-2.43); p <0.001]. Meanwhile, PTCL-NOS of the bones, soft tissue, and skin was associated with better overall survival [HR=0.57 (0.45-0.72); p <0.001] and lymphoma-specific survival [HR=0.43 (0.32-0.57); p <0.001]. These findings were statistically significant even after adjustments were made for other variables. This

suggested that PTCL-NOS survival was impacted by primary disease site for our subset of patients. Additional research is needed to validate these findings and determine the utility of using primary disease site for prognostication indices.

Figure 1: Kaplan-Meier: All stage (Stage I-IV) PTCL-NOS 5-year survival by Primary Disease Site



CANNABIS USE IS RELATED TO SLEEP QUALITY AND DURATION

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Background: Cannabis use has become increasingly predominant in the general population and cancer patients. Prior research has demonstrated mixed associations between cannabis use, sleep quality, and sleep duration. Few studies have used smartphone-based ecological momentary assessments (EMA) to examine proximal relationships between cannabis use and perceived sleep quality and duration. This study aimed to address this gap in the literature using a nationwide sample of adults.
Methods: Participants in the parent trial enrolled in a nationwide 28-day smartphone-based study that aimed to determine the effects of five study design factors (e.g., timing and frequency of assessments) on compliance with prompted EMAs. The current sub-study included 96 participants that reported using cannabis on at least one day during the study period. Each morning, participants were asked about prior day's cannabis use and sleep quality the prior evening ("How would you rate the quality of your sleep last night?"). Sleep quality response options were on a Likert-type scale for 14 days (i.e., 1=Very poor to 5=Very good) and a slider-type scale for 14 days (i.e., 0=Low-10=High). Participants also answered a question about sleep duration: "How many hours of sleep did you get yesterday?"
Results: Participants (n=96) were 46.5 years old on average (SD=12.3) and were mostly White (69%) and female (71%). Participants reported that they used cannabis on 12.0 (SD=9.0) out of 28 days on average. After accounting for covariates (i.e., age, sex, race), multilevel analyses indicated significant positive effects of cannabis use on sleep quality (both Likert-type and slider-type questions, p's<.05). A second multilevel analysis indicated that participants reported more hours of sleep on days that cannabis was used versus not used (β= .03, p<0.05). A likelihood ratio test indicated that the effect of cannabis use on sleep hours differed across participants (chi square=61.3, p<0.05).

Conclusions: In this national sample, cannabis use was associated with increased sleep duration and quality. This study provides new evidence about the impact of cannabis use on sleep using EMAs that minimize recall bias and highlights within-subject variation. Future research should incorporate objective measures of sleep quality and duration to identify mechanisms of this observed relationship and examine if this relationship exists specifically among cancer patients.
Funding: This study was supported by the Oklahoma Tobacco Settlement Endowment Trust (grant number R21-02) and the mobile health shared resource of the Stephenson Cancer Center via an NCI Cancer Center Support Grant (grant number P30CA225520).

DCLK1 PROMOTES CHEMORESISTANCE IN OVARIAN CANCER

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Ovarian cancer (OvCa) has a dismal prognosis in most patients because of its late-stage diagnosis and emergence of resistance to platinum-based chemotherapy. Current efforts to improve patient outcomes focus on developing novel treatment strategies to overcome chemoresistance. Doublecortin-like kinase 1 (DCLK1) is a serine/threonine kinase known to regulate cancer cell "stemness", epithelial-mesenchymal transition (EMT), disease progression in gastrointestinal and pancreatic cancers and drug resistance in lung cancer. The objective of this study was to evaluate the role of DCLK1 in regulating cisplatin-resistance (CPR), and assess the benefits of using inhibitors of DCLK1 as a novel treatment strategy to overcome OvCa recurrence. To this end, we used a combination of cisplatin-sensitive and resistant cell lines (OVCAR-8 and OVCAR-8CPR), pharmacologic inhibition (DCLK1-IN-1), genetic manipulation (CRISPR-Cas9 and over-expression), and novel silencing RNAs (siRNAs). We observed significant upregulation of DCLK1 in 3D spheroid OvCa cultures relative to 2D adherent cultures. Further, DCLK1 expression increased in CPR spheroids relative to sensitive control cells. DCLK1 inhibition was effective at re-sensitizing cells to cisplatin, reducing cell proliferation, migration, and invasion. Using kinase domain mutants, we demonstrate that DCLK1 kinase activity is critical for mediating CPR. Additionally, the combination of cisplatin and DCLK1-IN-1 showed a synergistic cytotoxic effect against OvCa cells in 3D conditions. Targeted gene expression profiling (Nanostring Tumor signaling 360) and pathway analysis revealed that DCLK1 inhibition in CPR OvCa spheroids significantly affected pathways related to ribonucleotide reductase signaling, cell death and survival, cell cycle, and EMT. Using an orthotopic CPR spheroid xenograft mouse model, we demonstrated in vivo efficacy of combination DCLK1 inhibition with cisplatin in significantly reducing tumor burden relative to a single agent alone. Collectively, our study shows that DCLK1 is important in regulating programs promoting CPR in OvCa. Targeting DCLK1 in combination with

existing chemotherapy could be a novel therapeutic approach to overcome CPR in a clinical setting.

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FOOD INSECURITY AND ITS RELATIONSHIP TO CANCER RELATED OUTCOMES

Grace Duininck

Objective: Food insecurity (FI) is defined as the disruption of food intake or eating patterns due to lack of money or other resources. 1 in 8 Americans lived in food insecure households in 2020, and the pandemic has increased FI among families with children and communities of color, who already faced hunger at higher rates. Population based studies have suggested that cancer risk is higher among individuals living in food insecure households, and there are currently no formal recommendations for FI screening in the oncological clinical setting. Although counterintuitive, FI is associated with obesity risk in women, which can be particularly problematic for cancers that are estrogen driven, such as endometrial cancer. The aims of this study were to estimate the prevalence and correlates of food insecurity among a cross sectional sample of gynecologic oncology patients. We hypothesized that patients who identify as Black or Hispanic, are uninsured/underinsured, or are obese at time of initial treatment will report higher rates of FI.

Methods: This was an IRB approved pilot study of all women seeking care for gynecologic cancer at a major academic center between September-December 2021. A three question survey was administered, using the validated "Hunger Vital Sign" food security screener, as well as a third question to screen for healthy food accessibility and affordability.

Results: A significant portion of patients reported FI, with 15%, 14% and 19% responding "yes" to questions 1, 2 and 3 respectively. Patients who reported FI were more likely to have Medcaid/Medicare, or to be uninsured ($p< 0.001$). Patients who reported FI were more likely to have cervical cancer (31 vs 23%, $p=0.08$), more likely to be non-white (29 vs 18%, $p=0.001$), and more likely identify as Hispanic/Latino (13 vs 5%, $p<0.001$). Average age between groups was 61 vs 55 when comparing food secure patients to food insecure patients ($p<0.001$). Average BMI was 33 vs 34 when comparing food secure patients to food insecure patients ($p=0.36$).

Conclusion: Although the exact mechanism by which food insecurity increases cancer risk is unknown, there are multiple possible associations. Low socioeconomic status (SES) is associated with fragmented or inconsistent access to care, which may result in inadequate cancer screening and prevention. Low SES is associated with unhealthy behaviors, such as tobacco use, physical inactivity, and excessive alcohol intake, which increase cancer risk. Severely constrained food budgets in food insecure households may complicate the cachexia and anorexia experienced by patients with cancer. FI can be a significant driver of cancer distress, which can lead to treatment non-adherence, increased use of outpatient and emergency department care, greater difficulty in decision making, and poorer quality of life. The high prevalence of FI among patients with cancer suggests that universal screening for FI among these patients is appropriate so as not to miss opportunities for intervention

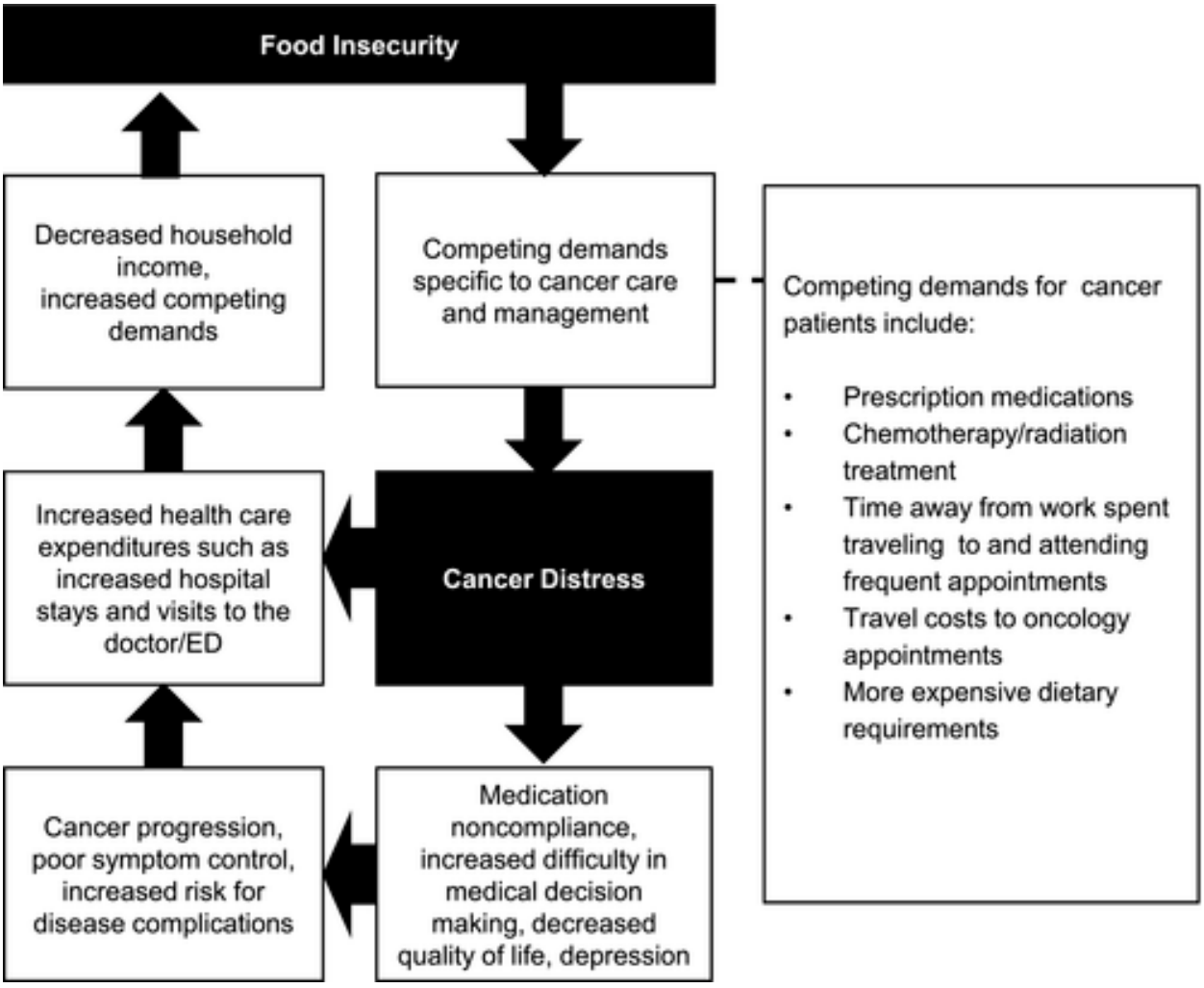

Figure 1: Complex relationship between food insecurity and cancer distress

A CASE REPORT OF HIGH FREQUENCY RHYTHMIC GAIT TRAINING TO ACCELERATE PROGRESS FOR A YOUNG ADULT 1.5 YEARS AFTER CEREBELLAR MEDULLOBLASTOMA

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Introduction: Long-term ataxia from cerebellar tumors and treatments compromises gait safety, physical activity and life participation. The pace of physical therapy (PT) progress can fall short of patients' goals, and neuroplasticity slows with time from brain injury. No clinical practice guideline directly addresses optimal PT approach, including the optimal visit frequency to restore independent gait. We describe the accelerated progress made by a brain tumor survivor with chronic ataxia when she transitioned from a traditional PT approach to high frequency (daily) outpatient treadmill training (TMT) and rhythmic auditory stimulation (RAS).

Case Description: A 19-year-old female sought neuro-oncologic specialty PT 1.5 years after grade IV cerebellar medulloblastoma resection, proton and chemotherapy. After 5 weeks of inpatient PT and 15 months of community outpatient PT 2-3 days/week, daily losses of balance continued to prevent safe gait with a walker. Ataxia was 25/40 on Scale for Assessment and Rating of Ataxia (SARA, 40=worst) and she could not tap her feet in time with a metronome. Gait speed (GS) was 0.63 m/s overground, step length coefficient of variation (CoV) on TM with trunk harness was 11% left/10% right. CT revealed cerebellar volume loss and dentate nuclei gliosis.

Intervention: PT 5 days/week focused on harnessed TMT (up to 25 min/session) with RAS, at highest safe gait speed with Borg RPE target 15/20 ("hard"). Resting heart rate 100-130 since tumor resection.

Outcomes: After 3-weeks of high frequency physical therapy (total 192 min TMT, max RPE 15/HR 165), GS improved 0.25 m/s to 0.88 m/s without loss of balance. Rate of gain will be presented graphically; greatest progress was week 1 (+0.14 m/s) but regressed (-0.08 m/s) each weekend until week 3. CoV improved 5% bilaterally and ataxia improved 4 points by SARA. She could tap to a beat and walk while reaching for objects or opening doors. After 10 more sessions at 2-3 days/week frequency, GS improved to 0.98 m/s. The patient rated her change (worst -7 to best +7) as +5 (quite a bit better). She transitioned from online to in-person college courses.

Conclusion: Even 1.5 years after brain tumor treatment, and after 15 months of traditional PT, this young adult survivor with severe chronic ataxia accelerated her gait progress in only 3 weeks of high frequency harnessed treadmill training (TMT) with rhythmic auditory stimulation (RAS). RPE and vitals suggest training volume was achieved by high frequency more than intensity, and 15 sessions was her threshold to retain gains. Research is warranted to compare efficacy, value and patient satisfaction with high frequency approaches to the same training volume provided at lower frequency, and with proper controls to quantify relative contributions of TMT and RAS.
Funding: None

IMPLICATION OF THE AKT/MTOR PATHWAY IN THE MECHANISM OF SHETA2 AND PALBOCICLIB SYNERGY IN CERVICAL CANCER CELL LINES.

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Cervical cancer is largely induced by high-risk human papillomavirus (hr-HPV), contributing to upwards of 95% of cervical cancer incidents. Tumor development progresses over years to decades, with the primary driver being expression of the two HPV oncogenes E6 and E7. These proteins canonically inhibit the tumor suppressors p53 and Rb. However, a variety of other pro-carcinogenic pathways are upregulated in hr-HPV cervical cancer including the PI3K/AKT/mTOR signaling pathway. Previously, our group has shown synergistic inhibition of cervical cancer cell growth using the novel 70-kDa heat shock protein (HSP70) inhibitor SHetA2 and the CDK4/6 inhibitor palbociclib. Cell cycle proteins affected by these drugs, including cyclin D1 and CDK4/6, have regulatory effects on the AKT pathway. We hypothesized that the synergistic effect of SHetA2 and palbociclib could be partially explained by AKT inhibition during combination therapy. In this study, effects of SHetA2 and palbociclib on phosphorylation of kinases in the AKT/mTOR pathway in cervical cancer cell lines were evaluated by western blot. Two mTOR complexes are involved in this signaling pathway, mTORC1 and mTORC2. The mTORC1 complex is downstream of AKT activation and is associated with increased signaling of pro-proliferation and pro-survival proteins. The mTORC2 complex is upstream of AKT and when activated through phosphorylation by mSIN1, phosphorylates AKT at the serine 473 (AKT-S473) site. We found that combination treatment of cervical cancer cell lines with SHetA2 and palbociclib decreased AKT-S473 phosphorylation, while individual drug treatments showed either no change or an increased level of phosphorylation at the S473 site. Our preliminary data support that these drug treatments cause a similar pattern of phosphorylation at the threonine 308 site of AKT (pAKT-T308). Overall expression of proteins in both mTORC complexes remained the same during individual treatments, however when used in combination there were significant decreases in expression of the mTORC1/2 complex scaffolding protein MLST8. The degradation of MLST8 caused by the combination treatment could partially explain both the reduction in pAKT-S473 phosphorylation and the synergistic effect of SHetA2 and palbociclib. These results show that, while neither SHetA2 nor palbociclib cause direct effects on AKT/mTOR signaling, inhibition of specific components of this pathway are associated with their synergistic effect.

E-CIGARETTE USE AND DEPRESSION AMONG AMERICAN INDIAN ADULTS WHO SMOKE

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Objective: In this cross-sectional study we examined the association of e-cigarette use status and history of depression among American Indian (AI) adults who smoke. Method: We used survey data from 375 adult AI smokers collected in 2016 at a tribally operated healthcare facility in northeast Oklahoma. Multivariable logistic regression was used to characterize the association between e-cigarette use and self-reported history of depression while adjusting for potential confounding. Results: In adjusted analyses, current (adj. OR 2.66, 95% CI 1.25 – 5.72) and former (adj. OR 2.38, 95% CI 1.36 – 4.26) e-cigarette users had higher odds of depression compared to never users. Additional independent associations with history of depression included strong cravings to smoke (adj. OR: 2.48; 95% CI: 1.25-5.21) and having a history of chronic disease (adj. OR: 2.46; 95% CI: 1.51-4.05) were also associated with history of depression. Age, sex, education, income, perception of e-cig harm, and confidence to stop tobacco use were not significantly associated with history of depression in this cohort. Conclusions: E-cigarette use among adult AI who smoke is independently associated with a history of depression. Whether e-cigarette use among people who smoke results from depression or whether depression results from combined use of e-cigarettes and cigarettes remains to be determined.

EFFECT OF 5-ALPHA REDUCTASE INHIBITORS ON POST-ABLATION THERAPY PSA

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Objective: The purpose of this study is to evaluate how treatment with a 5-alpha reductase inhibitor prior to ablation therapy for localized prostate cancer will affect PSA progression at the 3-month and 6-month mark compared to those not taking a 5-ARI prior to ablation therapy treatment.
Patients and methods: We performed a retrospective study using our ablation therapy database collected from patients undergoing either cryotherapy or HIFU for localized prostate cancer at our institution. Patients included 93 men undergoing primary treatment for low risk, localized prostate cancer not suitable for radical prostatectomy or radiation therapy based on comorbidities, who have > 10-year life expectancy. Of those patients, 9 patients were evaluated separately based on taking a 5-ARI for lower urinary symptoms prior to treatment. Patients were evaluated based on prostate cancer antigen (PSA) progression from the time of initial treatment to the 3-month and 6-month mark post-treatment. Percent of average decrease of PSA was used to evaluate progression, while treatment failure was defined as PSA > 2 of nadir.
Results: A total of 93 patients were included in our analysis. Median age was 71 and follow up time was 3 months and 6 months respectively. Of those undergoing cryotherapy, 5 out of 73 participants were taking a 5-ARI prior to receiving ablation therapy. Of those undergoing HIFU, 4 of 20 were taking a 5-ARI prior to receiving focal therapy. Mean percent drop in post-ablation therapy PSA for those not taking 5-ARI was 68.8% at 3 months. Mean percent drop in post-ablation therapy PSA for those taking 5-ARI was 65.5% at 3 months. At 6 months, mean percent drop in post ablation therapy PSA for those not taking a 5-ARI versus the 5-ARI group was 68.3% and 60.2% respectively. A greater PSA decrease was seen in the 5-ARI group than the control group when evaluating those undergoing HIFU therapy at both the 3-month (64.38% vs. 54.91%) and 6-month mark (58.33 vs. 54.56%), while those undergoing cryotherapy saw greater PSA decreases in those not taking a 5-ARI prior to treatment. Treatment failure occurred in 2/7 patients taking a 5-ARI prior to treatment, while treatment failure occurred in 4/80 patients not taking a 5-ARI (p-value= 0.04273).

Conclusion: Treatment with a 5-ARI prior to ablation therapy does not worsen PSA progression significantly. Treatment with a 5-ARI prior to cryotherapy does not improve outcomes at the 3- or 6-month mark, while treatment with a 5-ARI prior to HIFU may improve outcomes at the 3- and 6-month mark. Overall, 5-ARIs are safe and in some cases may result in better outcomes from ablation therapy for localized prostate cancer. More research is needed with a bigger sample size to further investigate.

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UNVEILING THE MECHANISMS OF TICRR DESTRUCTION DURING DNA REPLICATION

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DNA replication is a fundamental process for the biological inheritance of all living organisms. Initiation of this process is tightly regulated through two key steps: origin licensing and origin activation. Replication origins are licensed during G1 phase, and a small subset of licensed origins are selected for activation at G1/S phase transition. This transition is a highly regulated step of cell division, as its deregulation causes genome instability and cancer. TICRR/TRESLIN is a protein that is essential for two processes: activation of replication origins and preventing premature entry into mitosis. We recently showed that the level of this protein declines precipitously at the G1/S phase transition. We find that the destruction of TICRR/TRESLIN during S phase requires the proteasome, an E3 ubiquitin ligase called CRL4DTL, and PCNA, a replication factor that promotes DNA replication via binding to DNA polymerase. The mechanism by which TICRR is targeted to CRL4DTL is unclear. To further understand the role of PCNA and identify the sequence within TICRR that is required for its destruction, we conducted a series of experiments using siRNA-mediated knockdown, immuno-flow cytometry, and proximity ligation assays in HCT116 cells expressing endogenously tagged TICRR/TRESLIN. We have shown that TICRR physically interacts with PCNA, and we have identified a segment within TICRR is needed both for its interaction with PCNA and for its degradation. Our next step is to genetically test the functional importance of TICRR degradation for DNA replication and cell cycle control.

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DRUG REPURPOSING IN PANCREATIC CANCER, PRECLINICAL RESULTS

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Pancreatic cancer accounts for 8.2% of all cancer deaths with continuously rising incidence rate. Patients in later stages of the disease, representing the majority of presented cases, are typically offered a systemic treatment. Despite progress in systemic treatment in recent years, the 5-year survival rate of these patients remains low, a mournful 3%. These data necessitate further improvement in diagnostics and therapy, including more effective systemic treatments. We evaluated anticancer potential of Nelfinavir on pancreatic cancer cells in vitro. Nelfinavir is a protease inhibitor primarily used in treatment of HIV positive patients, available in peroral form, currently also studied for its radiosensitising property. Pancreatic cell lines S2VP10 and Panc1 were treated with Nelfinavir in two different concentrations (40uM, 20uM). Cell viability was used to determine the levels of induced cell death for each concentration and each cell line. We then used Western blot technique to identify the elevated markers of autophagy (LC3) and apoptosis (caspase III) in S2VP10 and Panc1 cell lines treated with Nelfinavir. The cell viability assay showed a statistically significant decrease in ATP levels consistent in both pancreatic cell lines and in treatment with both concentrations. We noted decrease in ATP of 56.22% in treatment with 40uM of Nelfinavir ($p < 0.0001$) and 23.1% in treatment with 20uM of Nelfinavir ($p = 0.0005$) in S2VP10 cell line and decrease in ATP of 32.3% ($p = 0.0034$) and 24.48% ($p = 0.0261$) in Panc1 cell line. Western blot results confirmed cell death. Repositioning of a drug is extremely time and cost saving. We proved a potent in vitro anticancer effect of Nelfinavir in two separate pancreatic cancer cell lines, including aggressive S2VP10 cells. Additionally, to emerging studies on radiosensitising properties of Nelfinavir in pancreatic cancer treatment, we point to its capacity to effectively induce cell death in pancreatic cancer cells in vitro.

UTILITY OF WORST PATTERN OF INVASION IN GUIDING ADJUVANT TREATMENT IN EARLY-STAGE ORAL CAVITY CANCER

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Introduction: There are several pathologic risk factors that influence post- operative management of early-stage oral cavity squamous carcinoma (OSCC). The worst pattern of invasion (WPOI), ranging from I-V, is a known prognosticator for OSCC, especially the presence of WPOI-5. Because it remains optional in pathology reporting, it is not widely utilized to guide adjuvant therapy of early stage OSCC. Our study aims to analyze clinical outcomes with early stage OSCC and WPOI-5 to determine whether WPOI-5 is an indication for adjuvant radiation therapy in this population.

Methods and Materials: This is a single- institution retrospective analysis of patients with early-stage OSCC (T1-2 Nx-N0 M0) and WPOI-5 who were either observed or treated with adjuvant radiation therapy. WPOI-5 was defined as tumor dispersion >/=1mm between tumor satellites. Tumor stage, as defined by the AJCC 8th edition, and histopathological features were collected from pathology reports at the time of initial surgery. Electronic medical records were used to collect information regarding patient demographics, adjuvant treatment and disease status. Median follow-up was defined as time from initial surgery to most recent follow-up. Median progression free survival (PFS) was defined as time from initial surgery to time of disease progression.

Results: We identified 4 patients meeting the inclusion criteria treated between December 2018 and December 2021 at our institution. Median follow up time was 36.7 months. All patients underwent partial glossectomy, and 3 patients also underwent selective unilateral neck dissection at the time of initial surgery. One patient underwent revision surgery due to positive margins on initial pathology, and subsequently had negative margins. All 4 tumors were well to moderately differentiated, with negative margins and absence of extra-nodal extension. 2 tumors demonstrated perineural invasion and none demonstrated lymphovascular invasion. Following surgery, 2 patients were observed and 2 underwent adjuvant radiation therapy (RT). RT dose was 60 Gy in 30 fractions. None of the patients received chemotherapy. At time of last follow up, all patients were alive and under active surveillance. Median PFS for the observation

cohort was 32.8 months. Both patients in the observation arm had recurred at time of analysis and all recurrences were locoregional. There have been no locoregional or distant recurrences in the adjuvant radiation cohort.
Conclusion: While our study is limited by small sample size, it demonstrates the impact of high risk WPOI on tumor behavior and disease outcomes. Additionally, the presence of WPOI-5 in early stage OSCC might be more relevant than historic poor prognostic factors, and this patient population may benefit from adjuvant radiation. A larger, multi-institutional retrospective analysis is required to further investigate this trend.

NECROPTOSIS-MEDIATED INFLAMMATION IS A POSSIBLE DRIVER OF HEPATOCELLULAR CARCINOMA IN AGING

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Chronic, low-grade inflammation that occurs with age (inflammaging) is one of the hallmarks of aging and a major risk factor for both morbidity and mortality in elderly. Hepatocellular carcinoma (HCC) is an age-related cancer with an increased incidence in people aged 50 or above. Chronic inflammation is a major contributor to the development and progression of HCC, and plays a crucial role in non-alcoholic steatohepatitis (NASH) arising from obesity, which is becoming a major risk factor for HCC in the United States. Despite this strong association between inflammation, aging, and HCC the molecular process responsible for inflammation or its role in age-related HCC is not clearly understood.

Necroptosis is a form of programmed cell death that plays a critical role in inflammation through the release of damage-associated molecular patterns (DAMPs) in a variety of diseases, including NASH. Previously, we have shown that *Sod1*$^{-/-}$ mice, which show accelerated aging and a dramatic increase in HCC incidence, display increased necroptosis and inflammation. Importantly, inhibiting necroptosis reduced inflammation in *Sod1*$^{-/-}$ mice providing evidence that necroptosis plays a role in inflammaging. We found that markers of necroptosis, liver inflammation, and NASH pathology (steatosis and fibrosis) increases with age in WT mice, and therefore we tested whether necroptosis contributes to age associated liver inflammation and NASH in old WT mice. To block necroptosis, we used mouse models in which either *Ripk3* or *Mlkl,* two key kinases in the necroptosis pathway, is globally knocked out. Our data showed that compared to age matched old (24-months) WT male mice, old *Ripk3*$^{-/-}$ or *Mlkl*$^{-/-}$ mice have significantly reduced levels of M1 proinflammatory macrophages, proinflammatory cytokines (*IL-6*, *IL-1*β, and *TNF*α) and chemokine (CCL2) in the liver. Similarly, NASH pathology that was elevated in old WT mice (relative to young mice, 6-month) was significantly reduced in old *Ripk3*$^{-/-}$ or *Mlkl*$^{-/-}$ mice, supporting a role of necroptosis-mediated inflammation in NASH development in aging. Interestingly, blocking

necroptosis also reduced markers of cell senescence (p16, p21), an important pathway implicated in inflammaging as well as HCC. Next, to directly test the role of necroptosis in NASH-driven HCC, *Ripk3*$^{-/-}$ and *Mlkl*$^{-/-}$ mice were fed an HCC inducing diet. Our results showed that absence of *Ripk3* or *Mlkl* significantly reduced liver inflammation and HCC incidence relative to control mice. Collectively, our data shows that necroptosis is a key mediator of inflammation in aging and HCC, and suggests that necroptosis could be targeted to prevent HCC development in the elderly.

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EXOSOME-BASED REDOX BALANCE MODIFIER FOR ANTICANCER THERAPY TO OVERCOME MULTIDRUG RESISTANCE CANCER

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Multidrug resistance (MDR), one of defensive mechanisms of cancer following chemotherapy, is a major hurdle in clinical treatment. Cancer cells sustain increased levels of reactive oxygen species (ROS) and maintain redox balance with antioxidants, including glutathione (GSH). Oxidative stress and ROS scavenging systems in MDR cancer cell are generally increased compared to non-MDR cancer cells. Therefore, the alternation of redox balance is a promising concept, and depletion of GSH to induce oxidative stress, leading to apoptotic cancer cell death is an applicable therapeutic target for non-MDR and MDR cancer cells. MDR cancer cells overexpress the efflux pump which needs an adenosine triphosphate (ATP). Oxidation therapy induces malfunction of mitochondria and a lack of ATP supply to the MDR pump. Herein, we developed benzoyloxy dibenzyl carbonate (B2C)-encapsulated exosomes (B2CEx), which bypass the P-glycoprotein pump to deplete GSH in MDR cells. B2CEx showed improved therapeutic effect by tropism, disrupting ROS balance, and malfunction of efflux systems *in vitro*. In the study of tumor xenograft models, B2CEx significantly suppressed tumor growth and induced apoptotic cell death with higher ROS levels without chemotherapeutics. Given its improved therapeutic activities, B2CEx offers translational potential for cancer therapy, including MDR cancer cells.

THE LABORATORY OF BIOMOLECULAR STRUCTURE AND FUNCTION AT OUHSC

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We would like you to know about the services in protein purification, protein structural studies, and molecular modeling available to OUHSC in the Laboratory of Biomolecular Structure and Function (LBSF). (BRC 406) manages both facilities. The LBSF has shakers for bacterial growth and chromatography equipment to make pure protein on the milligram scale. The purified protein can be used for biological, biophysical, or crystallographic studies. Training in the use of this equipment is available from Baylee Lacy, or she can do this work on a fee-for-service basis. Baylee can also do protein crystallization experiments and screen crystals for cryo conditions and diffraction quality with the LBSF in-house X-ray diffraction instrument. The LBSF sends crystals for the Stanford Synchrotron Radiation Lightsource for data collection six times a year. Dr. Mooers has continuously been the PI of general user proposals at SSRL for 23 years.

LBSF also provides crystal structure determination, refinement, validation, and deposition services in the Protein Databank. The LBSF also provides services in small-angle X-ray scattering and structure-based drug design. We do the latter via virtual screening using high-performance computing and eight GPUs for molecular dynamics simulations. The LBSF interfaces with the Center for Therapeutic Sciences that Dr. Matthew Hart leads. Dr. Mather leads the Molecular Modeling Unit of the LBSF; this unit specializes in rational structure-based drug design and in modeling long-range motions in a protein's structure that are vital to a protein's function.

Dr. Mooers can consult on how best to incorporate structural biology into a research program, and he can help write grant proposals that include structural biology. The LBSF currently serves 14 labs at OUHSC and four labs off campus. We seek to expand our local user base to at least 18 labs over the next three years. The LBSF is a Vice President of Research Core Facility and is part of the Biomolecular Structure Core Facility of the ß in Structural Biology. It is also partly supported by the Department of Biochemistry and Molecular Biology.

HOW TO QUIT SMOKING: TIPS FROM UNITED STATES VIETNAMESE HEALTHCARE PROVIDERS, COMMUNITY LEADERS, AND PAST TOBACCO USERS

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Significance: Among Asian populations in the United States (US), the Vietnamese ranks second highest in smoking prevalence. Smoking prevalence is even higher among US Vietnamese with limited English proficiency (LEP) because they cannot fully utilize smoking-cessation resources in English. This qualitative analysis of perspectives from US Vietnamese healthcare professionals, community leaders, and past tobacco users aims to explore advice and applicable techniques to help US Vietnamese smokers quit smoking – hence, improve their health outcomes and prevent cancer.

Methods: We conducted 16 in-depth interviews with 6 US Vietnamese healthcare providers, 5 community leaders, 3 past smokers, and 2 participants who were both healthcare providers and past smokers. The interviewees were diverse in age, sex, profession, and specialty. Interviews were recorded and transcribed verbatim. Data were analyzed using the MAXQDA program. Codes and themes are based on constructs and phases of the Phase-Based Model of smoking cessation which includes Motivation, Preparation, Cessation, and Maintenance phases.

Results: Some prominent advice that arose for the motivation theme was the need to have a firm determination to quit or a reason why smoking cessation is necessary (e.g., protecting the family from the harms of smoke, serving as a role model for others in the family, or avoiding negative heath consequences). Salient advice for the preparation and cessation phases included healthy approaches to coping with stress (e.g., meditation or going for a walk), physically avoiding smoking triggers, changing unmindful habits, and engaging in activities that distracted one from craving (e.g., playing chess or chewing a candy or gum). Gradually reducing the number of cigarettes smoked per day was also

indicated as a helpful strategy. In the maintenance phase, participants shared potentially helpful strategies for avoiding relapse, including exercising regularly, being prepared to cope with the potential peer pressure for smoking at social gatherings (e.g., setting respectful boundaries around other smokers), staying firm about the decision to quit as an important promise (e.g., to their children) to keep, and continuing to avoid craving triggers. A prominent strategy that is related to all 4 phases is to create an environment with repeated/continuous support from loved ones.
Conclusion: This qualitative study identified several factors that serve as useful strategies for US Vietnamese smokers with LEP to quit smoking, with the ultimate goal of improving their health outcomes and preventing cancer.
Keywords: smoking cessation, tobacco treatment, cancer prevention, Vietnamese population
Acknowledgement: The parent research project is supported in part by the NCI Cancer Center Support Grant (P30CA225520) awarded to the University of Oklahoma Stephenson Cancer Center (SCC), and a grant from the Oklahoma Tobacco Settlement Endowment Trust (R23-02). The parent project also uses the SCC Mobile Health Technology (mHealth) Shared Resource. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.
Conflicts of Interest: All authors declare no conflict of interest.

CD82 AFFECTS THE ANAEROBIC GLYCOLYSIS IN CANCER STEM CELL PROMOTING BREAST CANCER PROLIFERATION

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Background: Tetraspanin CD82 suppresses the progression and metastasis of multiple solid malignancies, and the loss and downregulation of CD82 expression have been reported in various types of carcinomas and sarcomas causing a dismal prognosis. Like other tetraspanins, CD82 inhibits tumor cell movement by influencing integrin-related cell biology processes, which is considered as its well-known working mechanisms during tumor progression and metastasis. Indeed, tumor progression attributes to the growth of primary tumors in situ to certain extents, while cancer cell metabolism affects the cell proliferation by rendering adequate energy supply. Additionally, the amplification of the small populated cancer stem cell greatly affects primary tumor relapse manifesting as tenacious drug-resistance. However, different from its suppressive impact on metastasis, the direct effect of CD82 on primary tumor remains to be determined. Therefore, we hypothesized that, at the tumor cell level, CD82 not only inhibits the aggressiveness of primary tumor but also modulates cancer stem cells by influencing the metabolism of basic nutrients. Here, to test this hypothesis, we conducted a series of experiments to determine the role(s) of CD82 in tumor metabolism.
Method: CD82-shRNA modified breast cancer cell lines (triple-negative MDA-MB-231 and ER-positive T-47D cell lines) and Cd82fl/fl; MMTV-Pymt+ transgenic mice were used in this study. Seahorse XF Glycolysis Stress Test Kit was performed to measure the capacity of the glycolytic pathway. The sphere formation assay was conducted to assess the stem cells' population residing in tumors and obtain cancer stem cells. Western Blot was to measure enzyme protein level in anaerobic glycolysis.
Results: The proliferations of human breast cancer cells in which CD82 was knocked down are faster, and the primary tumor growth of murine breast cancer in which Cd82 was ablated is also quicker. The oncosphere formation efficiency became elevated upon CD82 removal, so did the oncosphere size. Seahorse XF Glycolysis Stress Test indicated the reduced levels of glycolysis in CD82-silenced breast cancer cells, compared to the control breast cancer cells. The protein levels of lactate dehydrogenase B and pyruvate kinase M2 were increased in the breast cancer stem cells in which CD82 was knocked-down, compared to the control group.

Conclusion: CD82 affects the protein levels and functions of lactate dehydrogenase B and pyruvate kinase M2 in breast cancer stem cell during anaerobic glycolysis, which promotes the faster proliferation of breast cancer cells and quicker growth of primary breast tumor leading to poor prognosis.

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INFLUENCE OF STRUCTURAL FEATURES OF SQUARAINE DYES ON OPTOACOUSTIC INTENSITY

William M MacCuaig, Carly Wickizer, Richard S. Van, Megan R. Lerner, William E. Grizzle, Yihan Shao, Maged Henary, Lacey R. McNally

Surgical removal of cancers results in the most favorable patient outcomes. Resection margins may be tumor-positive in up to 70% of cases depending on cancer type, representing an unmet clinical need. Image-guided surgery often utilizes fluorescent dyes such as IR 800CW, but are limited to 8mm of depth and result in potential false-positive signal due to high blood binding. To overcome limitations, we are developing new contrast agents for Multispectral optoacoustic tomography (MSOT)-guided surgery to allow for greater depth of penetration and future potential of multiplexing of agents. To generate squaraine contrast agents, we prepared heterocyclic salts side arms refluxed with squaric acid to form 6 different compounds. The compounds differ only in halogenation of heterocyclic salts and inclusion of dual trimethylpropylammonium (TMAB) pendant groups. All squaraines were confirmed with NMR/spectrometry. MSOT and fluorescence were utilized to investigate the *in vitro* optoacoustic/fluorescence activity of the compounds. Computational modeling of squaraines through density functional theory was used to reveal quantum properties of the compounds including vibrational entropy, oscillator strength, and dipole moment. Compounds were administered orally in a murine model to confirm visualization capability with MSOT and fluorescence.

Squaraine dyes functionalized with heavier halogens (Br, Cl) exhibited higher optoacoustic activity than dyes with less heavy (F), or without halogen. Specifically, TMAB/Br functionalized squaraine exhibited 2.12 optoacoustic units *in vivo*, compared to 0.81, 0.58, and 0.44 for Cl, F, and no halogen compounds, respectively (all $p<0.001$). Inclusion of the dual TMAB groups increased optoacoustic activity. When comparing Br compounds with/without TMAB, the TMAB functionalized compound outperformed the counterpart significantly, (2.12 a.u. vs. 0.21 a.u., $p<0.001$). Fluorescence intensity *in vivo* between TMAB/Br and TMAB/Cl compounds were not significantly different ($3.07E^9$ vs. $2.81E^9$ counts), indicating that fluorescence signal does not necessarily predict optoacoustic activity. Computational modeling revealed heavy halogens and TMAB functionalized dyes exhibit increased vibrational entropy, oscillator strength, dipole moment, and presence of right-shifted absorbance peaks. *In vivo* studies in a murine

model confirmed that heavy halogen and TMAB functionalized dyes were visible in the gastrointestinal tract using both MSOT and fluorescence imaging.

Image-guided surgical removal of cancer yields best patient outcomes, but is currently limited by blood binding and imaging depth. MSOT is a potential candidate, but lack of contrast has hurt clinical application. This study focused on synthesis and evaluation of squaraine compounds as potential optoacoustic contrast to expand the potential of MSOT in a clinical setting for image guided surgery for cancer.

Work performed at the Department of Surgery (OUHSC) and the Department of Biomedical Engineering (OU-Norman)

INCREASED INCIDENCE OF BASALOID SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: A CONSEQUENCE OF NEW LIFESTYLES?

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Background: Basaloid squamous cell carcinoma (BSCC) is an extremely rare variant of squamous cell carcinoma (SCC) that has a predilection for the aerodigestive tract. Recently, 2 very aggressive BSCC cases were reported in long-term electronic cigarette users without other cancer risk factors. There is inconclusive data on whether BSCC or SCC has poorer prognosis. Here, we present the most in-depth and recent data from the Surveillance, Epidemiology, and End Results (SEER) database to understand changes in incidence and the prognosis differences between BSCC and SCC.
Methods: The SEER database was queried for head and neck BSCC and SCC from 2000 to 2019. Survival outcomes were analyzed using Kaplan-Meier methods. Data analyses were performed using SPSS 28.0.
Results: From 2000 to 2019, there were 1,503 cases of BSCC. The median overall survival was noted to be 112 months (95% CI 97 to 127), with 3-year survival being 72% for BSCC. In the same interval, there was a total of 61,630 cases for SCC. The median overall survival for SCC was 61 months (95% CI 60 to 62), with the 3-year survival being 60%. BSCC constituted 1.7% of all SCC reported between 2000 and 2009, and 3% of all SCC reported between 2010 and 2019.
Conclusion: Our initial data suggests that the incidence of BSCC has increased over the last decade. Although BSCC has more aggressive histopathologic characteristics, our data suggest that 3-year overall survival for BSCC is more favorable than SCC, which contrasts with previous literature. Further multivariate analyses are in progress. Differences in lifestyle, early detection and treatment, multiple comorbidities, and exposures to toxicants are potential explanations for these observed differences.
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IMPACT OF MMR STATUS ON OUTCOMES IN ADVANCED OR RECURRENT ENDOMETRIAL CANCER WITH BEVACIZUMAB USE

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Objectives: Targeted therapy with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor receptor A, has been shown to have activity in advanced and recurrent endometrial cancer, both as a single agent and in combination with chemotherapy. While effective targeted options exist for tumors with DNA mismatch repair deficiency (dMMR), options are limited for patients (pts) with proficient MMR (pMMR) tumors. Only approximately 30% of endometrial cancers demonstrate dMMR, highlighting the need for additional effective treatment therapies in the pMMR population. We aimed to investigate the impact of MMR status on outcomes in advanced/recurrent endometrial cancer with bevacizumab use.

Methods: We conducted a retrospective, single institution study of pts with advanced or recurrent endometrial cancer who received bevacizumab therapy between 2015 and 2022 and had MMR data available. MMR status was determined by immunohistochemical stains and/or next generation sequencing. Pts were included if they received 2 or more cycles of bevacizumab, either alone or in combination with systemic therapy. Progression free survival (PFS) and overall survival (OS) outcomes were compared between pMMR and dMMR groups using Kaplan-Meier survival estimates and Log Rank survival tests.

Results: 64 charts were reviewed. 42 pts met inclusion criteria. 35 and 7 pts were included in the pMMR and dMMR groups, respectively. Groups were similar with respect to patient age, BMI, performance status, and tumor histology ($p>0.05$). Number of lines of prior systemic therapy, prior radiation, and subsequent systemic therapy usage after bevacizumab, including subsequent immunotherapy, was not significantly different between groups ($p>0.05$). Bevacizumab was used for recurrence in 85.7% of pts and for advanced or chemo naïve endometrial cancer in 14.3% of pts in each group ($p=1.00$). Bevacizumab was administered as a single agent (28.57%), with carboplatin and paclitaxel (16.67%), as part of a clinical trial (52.38%), or as maintenance therapy

(2.38%). Groups were similar with respect to the type of bevacizumab administration (p=0.875). Median PFS was 10.3 months (95% CI: 6.1, 20.3) among the pMMR group and 9 months (95% CI: 3.4, incalculable) among the dMMR group (p=0.912). There was no significant difference in OS between the dMMR and pMMR groups (p=0.087), however, a potential trend towards improved OS was seen in the dMMR group. Due to small sample size, we were unable to clearly demonstrate OS of pts with dMMR status. Median OS of pts with pMMR status was 22 months (95% CI: 13.4, 61.9).
Conclusions: While limited by small sample size, a potential trend towards improved OS was seen in pts with dMMR advanced or recurrent endometrial cancer who received bevacizumab. Larger studies are needed to confirm the impact of MMR deficiency on survival outcomes in this population, as well as further investigate optimal timing for potential incorporation of bevacizumab into lines of therapy based on MMR status.
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CONTINGENCY MANAGEMENT IS ASSOCIATED WITH LOWER SMOKING RISK AND LONGER PERIODS OF SMOKING ABSTINENCE DURING A QUIT ATTEMPT

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Background: Smoking lapse is common for adults trying to quit smoking and prior research has indicated that women are less likely to achieve smoking abstinence than men. Monetary incentives (contingency management; CM) can increase initiation and maintenance of smoking abstinence. This study examined whether supplementing standard care (SC) with a CM intervention reduced smoking lapses, increased periods of abstinence, and if gender moderated the risk of recurring smoking episodes.

Methods: Data collected from a randomized controlled trial that assigned participants to SC (counseling+pharmacotherapy; *n*=148) or SC plus a low-cost CM intervention (*n*=147) were used for this study. Participants completed ecological momentary assessments of their smoking behavior for 28 days post-quit (*M*=21.3 days, *SD*=8.5). The analysis sample included participants who reported abstinence for at least 24 hours (n_{SC}=100; n_{CM}=124; M_{Age}=48.2 years, SD_{Age}=11.7, 64% Female; 80% with annual family income less than $21,000). Data were formatted for fitting multilevel recurring episode survival models. Episodes of smoking were defined as spans of concurrent smoking days.

Results: After an initial 24-hours of abstinence, participants on average self-reported initiating 2.2 smoking episodes (min=1, max=6), each spanning a median of 3 days (min=1, max=28). Results indicated CM participants were 57% less likely to initiate a smoking episode on a given post-quit day compared with SC participants (*HR*=0.4, 95% *CI*[0.3, 0.6]). Gender was not uniquely associated with time until recurring smoking episodes (*HR*=0.9, 95% *CI*[0.5, 1.6]), but it moderated the association between intervention type and time until recurring smoking episodes (*HR*=2.6, 95% *CI*[1.2, 5.6]). Whereas men and women who received SC were relatively similar in their likelihood of initiating smoking episodes (Median=3 days until each lapse), women who received CM were more likely than men who received CM to initiate smoking episodes sooner ($Median_{Women}$=5 days, $Median_{Men}$=16 days).

Conclusions: These findings suggest that supplementing SC for smoking cessation with low-cost CM incentives may be particularly effective for men in terms of reducing recurring smoking lapse risk and lengthening the time between smoking lapses during a quit attempt. Future research should collect objective measures of daily smoking abstinence (e.g., remote CO) and identify ways to increase periods of smoking abstinence for female participants.

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ASSOCIATION OF CYCLIN D1 AND FILAMIN A INTERACTION IN THE MECHANISMS OF SHETA2 AND OLAPARIB AGAINST OVARIAN CANCER

Laura Mortan

Ovarian cancer is the fifth most frequent cause of death and the leading cause of death in women diagnosed with gynecological cancers. Most cases of ovarian cancers are diagnosed late stage after the cancer has left the primary tumor site. Standard of care is usually debulking surgery followed by frontline cancer therapeutics to get undetectable levels of cancer within the body. After levels are undetectable, maintenance therapy is given to keep the cancer from coming back. Olaparib is an approved maintenance therapy drug commonly used in the clinical setting. SHetA2 is a new investigational drug which has shown efficacy without toxicities in an ovarian cancer maintenance therapy animal model. One of the known mechanisms of SHetA2 in ovarian cancer is through reduction of cyclin D1. Cyclin D1 is an important cell cycle regulatory protein that facilitates the G1 to S phase transition. The cyclin D1 complex has been shown to phosphorylate filamin A which is a vital scaffolding protein that is important for cell adhesion and migration. The objectives of this study were to evaluate the potential of SHetA2 to enhance olaparib treatment in ovarian cancer while studying the effect of drug treatment on cyclin D1 and filamin A. The effects of SHetA2 and olaparib on OV90 and OVCAR-8 ovarian cancer cell lines were evaluated using MTT assays and imaging of immunocytochemistry. Both cell lines were growth inhibited by SHetA2 or olaparib in dose- and time-dependent manners. We found that both SHetA2 (10 μM) and olaparib (160 μM) reduced total cellular cyclin D1 levels. After controlling for total cyclin D1, we determined that both SHetA2 and olaparib reduced cyclin D1 colocalization with filamin A at the plasma membrane. The results suggest that the complementary growth inhibition of SHetA2 and olaparib on ovarian cancer cell lines is associated with the reduction of cyclin D1 and its colocalization with filamin A.

MULTI-PARAMETER STRUCTURAL ANALYSIS OF MULTICELLULAR TUMOR SPHEROIDS USING OPTICAL COHERENCE TOMOGRAPHY

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The multicellular tumor spheroids (MCTs) have been an advanced tumor model for cancer research as they serve as an ideal intermediary between *in vitro* and *in vivo* models. Optical coherence tomography (OCT) had been demonstrated as an ideal tool for analyzing the change of structure and tissue distribution within MCTs. Currently, intensity-based OCT images are primarily used to observe morphological changes and detect necrotic tissues by analyzing the intrinsic optical attenuation coefficient within MCTs. In this study, we utilized multi parameters including the intrinsic optical attenuation coefficient, surface uniformity and roughness, and texture character extraction to provide a comprehensive analysis for multicellular tumor spheroids (MCTs). We cultured OVCAR4, OVCAR8, and Panc02-H7 MCTs with 5,000 tumor cells. Particularly, OVCAR4 MCTs were treated by inhibitors of 2-Methoxyestradiol, AZD1208, and R-Ketorolac with concentration of 1, 10, 25 μM and Pan02-H7 MCTs were co-cultured with fibroblasts. Our result demonstrated that OCT-based multi-parameter images not only revealed information on morphology changes and necrotic tissues dynamics but also provided the characterization of tissue distribution within MCTs induced by the collagen and inhibitor treatments. We concluded that OCT-based multi-parameter structural image was a promising analysis tool for detecting and tracking the tissue change and progression within MCTs in cancer research.

Keyword: Multicellular tumor spheroid, optical coherence tomography, intrinsic optical attenuation coefficient, uniformity, roughness, texture character extraction

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NOVEL MOLECULAR PATHWAY FOR CHROMOSOME 12 TRISOMY ACQUISITION

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The vast majority of cancers display a high rate of chromosomal instability leading to aneuploidies. Most tumors are aneuploid, ranging from ~25% in some tumor types to ~99% in others. Whole-chromosome missegregations are detected during the progression of invasive carcinomas and are proven to contribute to drug resistance and poor prognosis. One of those examples is the gain of entire copy of chromosome 12 (trisomy 12). It is a common cytogenetic abnormality observed in patients with lymphocytic leukemias and small lymphocytic lymphomas. Trisomy 12 is also often detected in patients with testicular and ovarian germ cell tumors. Patients with trisomy 12 have an intermediate prognosis and show higher incidences of secondary cancers. Studies on human stem cells have proven that trisomies can be tumor-promoting. Human induced pluripotent stem cells (hiPSCs) offer a huge potential in replacing damaged tissues and organs. Our and others' work has shown that in culture, hiPSCs accumulate genetic aberrations, limiting their usefulness in therapy. One common abnormality is trisomy 12. Chromosome 12 (chr12) trisomic cells become dominant in the culture, but how the trisomy arises and how it becomes dominant remains unknown. Though trisomic cells proliferate slightly faster than their diploid precursors, the difference in growth rates is insufficient to account for the rapid dominance of trisomic cells. To understand the potential mechanism of trisomy 12, we performed fluorescent in-situ hybridization (FISH) and whole chr12 paint in the transition passages where trisomic cells gain dominance. Surprisingly, analyses of transition passages cells in anaphase showed many cells with three signals from chr12 oriented to one pole and two oriented to the other pole. We also detected single, potentially unpaired chr12 chromatids apart from aligned chromosomes in metaphase cells. These data suggest that transition passages show a high proportion of cells entering mitosis with two normal chr12's and one half chr12 (single chromatid). We hypothesize that during the transition passages, chr12 missegregates into micronuclei (MN) in multiple cells. We found that chr12 is found in MN more often than expected by random chance. DNA in

these MN fail to replicate. Thus when the cells enter the next mitosis, they contain the two normal copies of chr12 from the main nucleus and the incorporated chr12 from the micronucleus. These findings implicate a completely novel mechanism of aneuploidy that may be of profound importance in genome instability in stem and cancer cell biology.

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THE RELATION BETWEEN CANCER RISK BEHAVIORS, PARTICIPANT CHARACTERISTICS, AND COVID-19 VACCINATION STATUS

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Background: Although the COVID-19 vaccine is readily and freely available in the United States, many individuals feel hesitant or refuse to receive the vaccine. This research aimed to identify associations between cancer risk behaviors, demographic characteristics, and COVID-19 vaccination status.

Methods: Participants were 485 adults that enrolled in a nationwide study to examine the effects of five different factors on compliance with daily smartphone-based ecological momentary assessments (EMAs). Participants downloaded the *Insight mHealth Platform* smartphone application onto their personal Android phone and completed the baseline assessment and daily EMAs. The 20-30-minute baseline survey included questions about demographics and various cancer risk behaviors (i.e., smoking status, self-reported weight, physical activity, fruit and vegetable intake, problematic alcohol usage, and sleep) assessed via relevant measures (e.g., the *Self Rated Health Questionnaire, AUDIT-C, Behavioral Risk Factor Surveillance System)*. COVID-19 related questions (e.g., vaccination status, vaccine hesitancy) were also assessed. Logistic regression analyses were conducted to determine if specific cancer risk behaviors were related to COVID-19 vaccination status and vaccine hesitancy among those that had not been vaccinated. All analyses included age, race (recoded as White/non-White), sex, and education as covariates.

Results: Participants (N=485) were predominantly female (76.3%), White (70.5%) and were 48.2 (SD=12.4) years old on average. Average years of education was 14.5 (SD=2.2). Younger adults ($p<0.05$) and those with lower levels of education ($p<0.05$), were less likely to have received the COVID-19 vaccine. Furthermore, participants that self-reported weighing too much ($p<.05$), non-smokers ($p<.05$), and those that reported lower levels of physical activity ($p<0.05$) were more likely to be vaccinated. None of the other assessed cancer risk behaviors were related to COVID-19 vaccination status. None of the demographic variables predicted vaccine hesitancy.

Conclusion: Study results are complex. While some groups that had higher risk for serious adverse effects of COVID-19 infection were more likely to be vaccinated (e.g., older, overweight

or physically inactive adults), other groups with elevated risk for negative COVID-19 related outcomes (e.g., smokers) were actually less likely to be vaccinated. Future research should examine reasons for vaccine non-compliance in unvaccinated high-risk populations.

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MECHANISMS DETERMINING WHERE DNA REPLICATION INITIATES IN THE HUMAN GENOME

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The selection of replication origins is a defining characteristic of DNA replication in higher eukaryotes, yet its mechanism in humans has not been well-defined. In yeast, origin selection involves replication initiation factor (Sld3-Sld7) recruitment to origins during G1. In this study, we use Cut&Run to examine genomic binding locations for TICRR and MTBP, the Sld3 and Sld7 orthologs. We have constructed two HCT116 human colorectal cancer cell lines in which the endogenous TICRR or MTBP loci were tagged at their carboxy-termini with mClover. Using these cell lines, we have shown that TICRR and MTBP genomic binding sites can be mapped using Cut&Run with anti-GFP antibody. We mapped TICRR and MTBP binding throughout the cell cycle by performing experiments in asynchronous, G1, or G2-arrested cells. Peaks of TICRR and MTBP binding frequently overlap at Ini-seq replication origins. Additionally, our results show HCT116 TICRR and MTBP peaks overlap with MTBP peaks previously defined (Kumagai et al. Cell Rep. 2020) in a DLD-1 cell line. Interestingly, our data show that TICRR and MTBP binding patterns are less defined in asynchronous cells than G1, possibly due to cell cycle phase-specific recruitment of TICRR-MTBP to replication origins in human cells.

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NECROPTOSIS EFFECTOR MLKL REGULATES LIVER METABOLISM AND INFLAMMATION IN NON-ALCOHOLIC FATTY LIVER DISEASE

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Non-alcoholic liver disease (NAFLD) is fast becoming the most common liver disease with the rising prevalence of obesity and metabolic syndrome. NAFLD covers a spectrum liver disease ranging from simple fatty liver (steatosis) through the more aggressive non-alcoholic steatohepatitis (NASH) to more severe chronic liver diseases, such as cirrhosis and hepatocellular carcinoma (HCC). With nearly 45% of individuals with steatosis progressing to NASH, NASH related HCC is reported to have increased by 68% in the past decade. Unfortunately, there are currently no effective treatments for NASH due to the complexity of the disease pathology.

Unresolved inflammation is a key player in the progression of the NASH pathology, which is a major risk factor for HCC. Necroptosis is a programmed cell death pathway that promotes inflammation and is reported to be activated in the livers of patients and mouse models of NAFLD/NASH. Studies have shown that inhibiting necroptosis by targeting RIPK3, (upstream kinase of the necroptosis effector MLKL), reduces hepatic inflammation and liver fibrosis in diet-induced mouse models of NASH. However, recent studies suggest that RIPK3 is involved in other cellular processes such as apoptosis, inflammasome activation and lipid metabolism. Therefore, we tested whether inhibiting/blocking MLKL, the effector molecule promoting necroptosis, will reduce hepatic inflammation and fibrosis in NAFLD.

For the study, we used wild type (WT, litter mates), *Mlkl*$^{-/-}$ and *Mlkl*$^{+/-}$ mice and were fed a control diet or a NASH inducing diet (NID) for 6 months. WT mice fed NID developed obesity, hepatic necroptosis, hepatic inflammation, steatosis, and liver fibrosis relative to WT mice fed control diet. *Mlkl*$^{-/-}$ and *Mlkl*$^{+/-}$ mice fed NID exhibited reduced body weight gain and decreased hepatic inflammation (Kupffer cell clusters, proinflammatory cytokines) and improved insulin sensitivity relative to WT mice fed NID. Surprisingly, markers of fibrosis were similar in WT, *Mlkl*$^{-/-}$ and *Mlkl*$^{+/-}$ mice fed NID. Total triglyceride content in *Mlkl*$^{-/-}$ and *Mlkl*$^{+/-}$ mice fed NID were significantly

higher than WT mice fed, however, lipid droplet size was smaller in *Mlkl*$^{-/-}$ and *Mlkl*$^{+/-}$ mice compared to the large sized ones in WT mice. Proteomics analysis of the liver tissues revealed the impact of *Mlkl* deficiency on glucose, lipid, and mitochondrial metabolic pathways. In addition, mitochondrial dynamics were altered by *Mlkl* deficiency.

Our study identified a key role of necroptosis effector MLKL in regulating liver metabolism, inflammation, while having little effect on liver fibrosis. Targeting MLKL and its downstream pathways therefore emerges as a novel opportunity in drug discovery approaches to treat NASH, and thus arrest disease progression.

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PROBING DISPARITIES IN EXPOSURE TO CIGARETTE SMOKING CONTEXTS USING COMPUTER VISION

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Background: High rates of smoking and poor cessation outcomes persist among many minoritized and underserved groups (i.e., women, low SES, racial and sexual minority groups). Numerous potential explanations for tobacco use inequities have been posited, but less attention has been paid to the environments that these groups are exposed to in everyday life, how daily environments differ between groups, and the potential influence specific environments may have on smoking behavior. In the present analysis, we used a novel machine learning algorithm developed and validated in our prior work (Engelhard et al., 2021) to examine differences in exposure to environments where smoking is allowed or the risk of smoking is high.

Methods: Daily cigarettes smokers residing in Durham, NC (N = 48) completed a 14-day ecological momentary assessment (EMA) protocol during which they were asked to photograph their current environment each time they smoked and following six random prompts throughout the day. An out-of-sample convolutional neural network model based on MobileNetV2 was pretrained on the ImageNet database and then trained to predict: (1) The probability that smoking was permitted; and (2) The probability of actual smoking based on the photograph and other contextual information. Mixed effect models were then used to examine overall differences in algorithm-predicted probabilities as a function of nicotine dependence, gender identity, race, sexual orientation and SES, as well as whether these effects differed across context types (i.e., smoking not allowed, smoking allowed but no active smoking; smoking allowed and active smoking taking place).

Results: The only main effect of demographic characteristics was a relatively weak effect indicating higher algorithm-predicted smoking risk for men relative to women (p = .039). Interactions with context type revealed stark differences in both outcomes as a function of nicotine dependence (Permitted: p = .032; Smoking: p = .030), race (Permitted: p = .035; Smoking: p = .048), and sexual orientation (Permitted: p = .005; Smoking: p = .005). In all cases, effects revealed less separation in algorithm-predicted risk between contexts in at-risk and minoritized populations. No significant interactions emerged for gender identity or SES.

Conclusions: Findings indicate that individuals with higher nicotine dependence and those who are members of certain minoritized groups are exposed to substantially different environments with regards to smoking permissiveness and risk of smoking. Surprisingly, these differences were not driven by higher predicted risk for smoking or smoking permissiveness across all contexts. Instead, effects revealed reduced differentiation between contexts, largely driven by increases algorithm-predicted risk in contexts where smoking was not allowed. This lack of differentiation between smoking and non-smoking environments offers a potential new insight into smoking disparities.

COMBINATION OF ATR AND PARP INHIBITION SYNERGIZES TO MODULATE DNA DAMAGE REPAIR AND AMELIORATES THERAPEUTIC RESPONSE IN CERVICAL CANCER

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Cervical cancer (CC) is the fourth most common malignancy of women worldwide with significant cancer-related mortality that accounts for over 310,000 deaths per year. Current chemoradiotherapy treatment strategies induce DNA damage, activate DNA damage repair pathways (DDR), and result in cell death by exploiting cells compromised by oncogenic strains of the human papillomavirus (HPV) which impair p53-associated DDR pathways. The objective of this study is to investigate the impact that dual targeting of DDR pathways modulated by Ataxia Telangiectasia and Rad3-related kinase (ATR) and poly (ADP-ribose) polymerase (PARP) has in improving the therapeutic response in CC. The cytotoxicity of ATR inhibition (AZD6738) and PARP inhibition (AZD2281) in HPV - positive CC cell lines (CaSki and SiHa were evaluated. Simultaneous treatment (AZD6738+ AZD2281) and AZD2281 pretreatment were additive and antagonistic respectively; whereas AZD6738 (ATRi) pretreatment followed by AZD2281 (PARPi) treatment was synergistic in CC cells. AZD6738 pretreatment drug combination also facilitated highly favorable dose reduction indices for AZD2281 in both cell lines, a clinically significant finding. AZD2281 increased H2AX phosphorylation which was further increased by AZD6738. PARP inhibition-induced Rad-51 foci formation was reduced by AZD6738 suggesting inhibition of homologous recombination. The combination of AZD6738 and AZD2281 induced cell cycle arrest in both cells and significant tumor growth reduction was observed *in vivo*. These preclinical findings suggest the combination of AZD6738 and AZD2281 is a promising strategy to enhance tumor cell death in HPV-positive cervical cancers most notably with novel synchronization of the ATR and PARP inhibiting agents.

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QUANTITATIVE ANALYSIS OF OVARIAN CANCER-DERIVED EXOSOME TROPISM

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Exosomes, one of the subtypes of extracellular vesicles, range from 50 to 200 nm in diameter and regulate cell-to-cell communication in the biological and pathological processes. Although exosomes derived from tumors have various functions in cancer progression, resistance, and metastasis through cancer exosome-derived tropism, there is no quantitative information on cancer exosome-derived tropism that will be beneficial to guide cancer therapy by inhibiting exosome release or uptake. Using two ovarian cancer cell lines (OVCA4 and OVCA8) that were transfected with the fluorescent protein (mkate2), tropism of cancer cell exosomes was quantified by measuring the release of exosome number from “parent” ovarian cancer cells and determining the uptake of these exosomes amounts into “parent” ovarian cancer cells, 3-D spheroids, and tumors from tumor-bearing mice models. An OVCA4 cell releases about 50 to 200 exosomes, and single OVCA8 cell secretes about 300 to 560 exosomes. Multifold exosome uptake from ovarian cancer cells into the “parent” ovarian cancer was observed compared to non-cancer cells. In vivo tumor-bearing mice models, most exosomes (200 to 600 million) are home to the “parent” cell tumors. Quantification of the release of cancer-derived exosomes and the uptake of the exosomes into their “parent” cancer cells, displayed the target tropism of cancer-derived exosomes. These results will be beneficial for future diagnosis and therapeutic applications.

ASSOCIATIONS BETWEEN COGNITION AND GAIT SPEED DURING CHEMOTHERAPY IN WOMEN'S CANCERS

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Introduction: Cancer-related cognitive impairment (CRCI) interferes with executive function, processing speed, attention and visual memory; chemotherapy is a risk factor. Similar cognitive declines associate with worse gait in older adults. While less is known in cancer, fall risk is elevated for age; understanding CRCI-gait relationships could inform falls screening and interventions. To explicitly test cognition's influence on gait, patients can Walk With a secondary ("dual") task such as right-left Head Turns (WWHT) on verbal command. Any speed decline from usual pace is the dual task cost (DTC). Digit Symbol Substitution (DSS) tests processing speed and visual memory as boxes correctly filled in 90 sec using a visual key patients may commit to memory early. We aimed to explore associations between DSS, patient-reported memory and concentration deficits, and gait speeds as women's cancer patients receive neurotoxic chemo.

Methods: Secondary analysis of data from 18 women with gyn or breast cancer (age 63.11 ± 12.00 yrs) who completed ≥2 taxane/platinum cycles in a prospective neuropathy feasibility pilot. Gait speeds were from repeated walks on a 20-ft pressure-sensing walkway in 3 conditions: usual (UP) and fast pace (FP), and WWHT. DTC (%) = [(UP– WWHT speed)/UP] X 100. Cognition was NCI-CTCAE Patient-Reported Outcome (1) Severity & (2) Interference with daily activities from (1) Memory or (2) Concentration issues. DSS was # of boxes completed in 1st or 2nd 45 sec. We used Linear-mixed models to quantify associations between each gait speed (UP, WWHT, FP) or DTC and each cognition variable. Exploratory alpha was 0.05 without multiple comparison adjustment.

Results: Visit significantly associated with UP, WWHT, DTC gait variables (β=0.022, 0.032, -0.933, respectively) and $DSST_{Last45}$ (β=0.879) (p<0.008). UP, WWHT, FP, DTC associated with $DSST_{1st\ 45}$ (β=12.718, 18.197, 6.982, -0.179; p<0.0335). Only FP

associated with $DSST_{Last45}$ (β=8.067; p=0.0173). The odds of reporting memory decline during chemo decreased 51.5% with a 0.1 m/s increase in WWHT and increased 11.9% with 1% increase in DTC.
Conclusions: In hypothesis-generating work, right-left head turns gait speed associated with DSS performance, but only in the 1st 45 sec (primary DSS learning period). Fast gait speed associated with the entire DSS and we hypothesize that this reflects writing and processing speeds. The improvement anticipated with repetition of a new cognitive task (WWHT, DSS) was attenuated in this women's cancers sample, suggesting impaired learning. Surprisingly, usual pace gait increased with neurotoxic chemotherapy in these older women. Our results support further research on CRCI-gait relationships, to fill a gap in evidence-based screenings and interventions for CRCI and cancer-related falls.
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RELATIONS BETWEEN SLEEP, CANCER RISK BEHAVIORS, AND AFFECT

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Background: Sleep duration and quality may be associated with daily affect, and cancer risk behaviors. Smartphone-based ecological momentary assessments (EMA) have been used to broaden knowledge of complex multilevel relationships. However, few studies have utilized EMA methods to examine day-to-day associations among sleep, affect, and cancer risk behaviors in the general population.

Methods: The current study used data that were collected as part of a 28-day randomized controlled trial that examined factors that may impact compliance with daily EMAs. EMAs assessed yesterday's soda, fruit and vegetable, alcohol, and cigarettes used/consumed, and moderate and vigorous physical activity. In addition, EMAs assessed current happiness and stress with both Likert (0=strongly disagree, 4=strongly agree) and slider type questions (0-10, representing none to high) for each affect item, respectively. Sleep duration (0-12 or more hours) and quality of sleep (Likert scale (0=very poor, 4=very good) or a slider scale (0-10, representing low to high)) were assessed daily. Generalized multilevel models estimated the relationships between aggregated daily happiness and stress and the previous night's sleep duration and quality. All models adjusted for sex, race, and age.

Results: Participants (N=452) were predominantly female (77.6%) and White (72.4%), with a mean age of 48.9. Sleep was not significantly related to next day cancer risk behaviors. Greater sleep duration was positively associated with next-day happiness and negatively related to next-day stress (all $p \leq 0.01$). The Likert-type sleep quality item was significantly related to the Likert-type affect items, such that greater sleep quality was related to greater next-day happiness, and lower next-day stress ($p \leq 0.01$). Moreover, the slider-type sleep quality item was significantly related to the happiness (positively) and stressed (negatively) slider-type items. No other analyses were significant.

Conclusion: Daily sleep quality and affect measured with Likert- versus slider-type items may not be equivalent when assessing the relationships between daily sleep and affect. Additional

research is needed to determine if there is significant value in choosing specific types of questions (e.g., slider versus Likert-type) in behavioral research involving sleep and affect.
Funding: This study was supported by the Oklahoma Tobacco Settlement Endowment Trust (grant number R21-02) and used the mobile health shared resource of the Stephenson Cancer Center via an NCI Cancer Center Support Grant (grant number P30CA225520).

FABRICATION OF G-BN NANOCOMPOSITES FOR LABELING BREAST CANCER CELLS TO IMPROVE CANCER IMAGING TECHNIQUES

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Cancer remains a major challenge for the twenty-first century. Although modern medicine has had several advances in cancer research, there is still an urgent need for more efficient techniques for cancer diagnosis, monitoring, and treatment. There are several intrinsic constraints for cancer cell molecular imaging such as photobleaching, autofluorescence, and a lack of sensitivity and specificity, however, these challenges can be overcome by an emerging technology called 'Raman spectroscopy'. Every atom inelastically scatters photons in a way unique to that material. Just as fingerprints are unique to individuals, this inelastic scattering is unique to each element or material. Raman spectroscopy studies molecular vibrations by detecting characteristic frequency shifts within a molecule to provide molecular information for any sample. Surface Enhanced Raman Spectroscopy (SERS) uses nanoparticles to enhance Raman signals. Graphene Quantum Dots (GQDs) and Hexagonal Boron Nitride nanosheets are novel nanoparticles that possess exceptional optical and electronic properties. Each have individually shown great promise as nanoparticles for bioimaging application [1]. This project aims to combine these two components as G-BN nanocomposites for SERS applications, which can be used to selectively and specifically image breast cancer cells. GQDs have been prepared using a bottom-up approach using naturally available bio-renewable rice grains. G-BN solution have been synthesized by dispersing HBN sheets in a Poly(diallyl dimethylammonium) (PDDA) aqueous solution containing NaCl, followed by sonication. This mixture was dispersed in a solution of GQDs and sonicated to obtain the nanocomposites. The prepared nanocomposites along with the GQDs and HBN sheets have been characterized using Raman, Fourier Transform Infrared Spectroscopy (FTIR), UV-Visible Spectroscopy (UV-Vis), and Transmission Electron Microscopy (TEM) to confirm successful preparation of the nanocomposites and understand their bonding mechanisms. After fabrication of the G-BN sheets, a 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) cell viability test will be performed to confirm the biocompatibility of the composites [2].

The unique optical properties achieved from the combination of HBN and GQD nanoparticles can provide new knowledge for SERS label fabrication, which will facilitate

rapid and accurate cancer imaging. Zero studies have leveraged the known synergy between GQDs and HBN for fabricating highly fluorescent SERS nanoparticles. This research fills that void. By employing a novel material that effectively labels breast cancer cells *in vitro*, we will revolutionize cancer imaging techniques while providing an avenue for the clinical adaptation of SERS and beyond.

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INCREASED MUTAGENICITY OBSERVED IN OKLAHOMA VAPING POPULATION

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Background: Electronic cigarettes (e-cig) are promoted as a safer alternative to tobacco smoke and are considered a potential tool for smoking cessation and harm reduction strategy. E-cig aerosol contains nicotine, ultrafine particles, volatile organic compounds, and heavy metals. Recent studies suggest that e-cig use increases inflammation, oxidative stress, DNA damage, and the excretion of a significant number of carcinogenic chemicals including, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, acetaldehyde, acrolein, benzene, N, N-dimethylformamide, lead, cadmium, nickel, and chromium in the user's urine. Yet, no studies have investigated the effect of e-cig use on urine mutagenicity in the real-life vaping population.

Aim: Assess the potential mutagenicity compound present in the vapers and non-vapers urine.

Methods: Following IRB approval, 12 exclusive vapers and 10 non-vapers were recruited for this study. Exclusion criteria include, ≥6 ppm exhaled carbon monoxide, urine positive for cannabis or pregnancy and unstable psychiatric condition. Salivary cotinine was quantified by ELISA (Salimetrics). Urine was extracted using the Amberlite XAD-2 column (Millipore-Sigma) and mutagenicity was assessed using the Ames Modified ISO Bacterial Strain Kit (EBPI) with and without S9 fraction. Data were analyzed by student t-test.

Results: Exhaled carbon monoxide (mean ± SD: 1.8 ± 0.9) confirmed that all the participants were absent from smoking. The salivary cotinine assay showed median saliva cotinine was 727 ng/mL for vapers and 6.3 ng/mL for non-vapers ($p \leq 0.0001$), this confirms participants vaping history. We observed that the urine of 5 out of 12 vapers (42%) and 1 out of 10 (10%) non-vapers induced mutations in TA100 bacterial strain after incubation with S9 fraction. These data show that the urine of vapers contained procarcinogenic and/or carcinogenic compounds that cause base pair substitution mutations in the TA100 bacterial strain.

Conclusion: Our data reveal for the first time, that e-cig users are systemically exposed to mutagenic chemicals that are able to cause significantly more mutations than non-vapers. Further studies are warranted to fully understand the impact of e-cig use and its health implications.

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COLLAGENASE -IV RESPONSIVE ACTIVE TARGETED SILICA NANOPARTICLES FOR PANCREATIC CANCER DETECTION BY MULTISPECTRAL OPTOACOUSTIC TOMOGRAPHY

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Purpose: Pancreatic ductal adenocarcinoma (PDAC) is the most lethal disease and the leading cause of cancer death worldwide. The survival rate of patients with this form of cancer is about 8%. The physiological barrier of the tumor microenvironment composed of a dense stroma and disorganized blood vessels creates a barrier for early identification and treatment of this deadly disease. In recent years, nanoparticle-based controlled delivery systems were developed to exploit the pathophysiology of biological systems such as acidic tumor microenvironment or the altered tumor-specific enzymes to improve the diagnosis and treatment efficacy. Here, we demonstrate the collagenase IV-mediated tumor site-selective release of the IR-780 imaging probe from the MSN-Gel-SDC1 nanoparticles, revealing the feasibility of the collagenase IV (MMP-9 and MMP-2) responsive target specificity for diagnosing pancreatic cancer by multispectral optoacoustic tomography (MSOT) imaging.

Methods: Mesoporous silica nanoparticles (MSN) with wormhole pore topology were synthesized and were characterized by dynamic light scattering (DLS) and transmission electron microscopy (TEM). The surface of MSN was conjugated with Gelatin-A and B to obtain MSN-Gel. The MSN-Gel particles were loaded with propidium Iodide (PI) or IR780 infrared imaging dye. The MSN -Gel surface was further conjugated with Syndecan-1 (SDC1) to improve the target specificity to release imaging cargo from the nanoparticles. Female athymic mice were orthotopically implanted with S2VP10 tumor cells. After a week of tumor implantation, mice were intravenously injected with MSN-Gel-SDC1 nanoparticles containing IR780 dye and were imaged with MSOT and AMI.

Results: In the current study, Mesoporous silica nanoparticles with 27 nm diameter were synthesized. The Gelatin-A and B crosslinking on the surface of MSN particles as a gatekeeper was developed that could degrade upon contact with collagenase IV in the tumor microenvironment. The conjugation of SDC1 further improved the tumor specificity. The athymic mice orthotopically implanted with S2VP10 cells closely resemble human PDAC. Our results demonstrated that intravenous delivery of MSN-Gel-SDC1 nanoparticles could enzymatically degrade Gelatin and release IR780 at the tumor site and conjugation of SDC1

further improved the tumor specificity to detect the orthotopically implanted pancreatic tumors ($p<0.0001, n=5$).

Conclusion: Due to the lack of effective screening tools, PDAC has the lowest survival rate and limited therapeutic efficacy for current FDA-approved drugs compared to other malignancies. Innovative technologies to develop engineered nanoparticles with active targeting moiety and dynamic imaging technology can overcome these limitations. Implementing such systems can enhance PDAC detection that can be translated into the clinic to improve health care.

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GENOME-WIDE SCREEN FOR NOVEL DNA REPLICATION FACTORS

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During each round of cell division, cells must faithfully duplicate their DNA. DNA replication occurs at tens-of-thousands of individual sites or "origins", along the DNA strands through a coordinated process. Genetic screens in yeast have been invaluable for the identification of proteins involved in DNA replication origin firing and DNA fork elongation. However, mammalian cells have a larger genome, a more complex chromatin environment, and are more intricately regulated. CDC45 is an evolutionarily conserved protein that is required for origin firing and DNA synthesis. To identify novel regulators of DNA replication initiation, we performed a genome-wide CRISPR-Cas sgRNA knockout screen in HCT116 cells expressing CDC45 fused to an auxin-induced degron. These cells display weakened DNA replication and impaired proliferative capacity with exposure to low levels of the plant hormone auxin. We used the BrunelloV2 sgRNA library containing 76,441 guides targeting 19,114 human genes to identify genes whose loss either enhanced or suppressed the proliferation phenotype of these cells with or without Auxin treatment. From this, we identified 14 candidate genes of interest that displayed statistically significant positive or negative enrichment. We are currently validating candidates through targeted sgRNA or siRNA knockdown.

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BARIATRIC SURGERY AND WEIGHT LOSS COUNSELING AMONG WOMEN WITH OBESITY AND ENDOMETRIAL CANCER

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Background: Women with obesity are six times more likely to die from endometrial cancer than women with a normal BMI. Studies suggest that bariatric surgery can help reduce the incidence of new cancer diagnoses and reduce the risk of recurrence. The barriers to uptake of this referral have been poorly studied but are suspected to be multifactorial and include a lack of education about bariatric surgery as a mechanism for weight loss.

Methods: Single-institution, retrospective review of all patients diagnosed with endometrial cancer from January 2013 to December 2020. Demographic characteristics, tumor characteristics, and treatment history were abstracted by chart review. Bivariate analysis was conducted using Fisher's Exact or Pearson's Chi-Squared test to analyze categorical variables and Student's T-test to analyze continuous variables. All P-values were two-sided and considered significant if <0.05.

Results: Six-hundred-fifty-five patients were included for analysis. The mean BMI was 42.42, 82.9% were White, and 70.7% were diagnosed with stage I endometrial cancer. Most were treated with standard-of-care surgery (89.7%), followed by hormonal therapy (6.7%), neoadjuvant chemotherapy (4.0%), and neoadjuvant radiation (1.6%). 98.6% of patients received educational handouts detailing the link between obesity and endometrial cancer. Other methods documented: 21.2% received weight-loss counseling, 3.9% referred to a dietician, and 3.2% referred to bariatric surgery. The mean weight change at 1 year post endometrial cancer diagnosis was a net loss of 0.62 kg.

Discussion: There was no difference in weight loss between those who received no weight loss counseling vs weight loss counseling vs referral to bariatric surgery (P = 0.6976). There is no difference in weight loss between groups that received surgery as their initial treatment and those that didn't (P = 0.2111).

Conclusions: Baseline bariatric surgery referral as well as weight loss counseling remains minimal amongst patients with endometrial cancer, despite the proven impact of both interventions.

TOBACCO USE AMONG AFGHAN REFUGEES RESETTLED IN THE U.S.

Munjireen Sifat, Brittany Zaring-Hinkle, Shawn C. Chiang, Darla Kendzor

Though smoking rates in the U.S. have declined to 12.5%, less is known about the rates of smoking within specific immigrant groups. Oklahoma welcomed 1,800 Afghan refugees after the U.S. military withdrawal from Afghanistan in 2021. Research in Afghanistan shows extremely high rates of smoking (up to 40.6%) among males. Thus, the purpose of this study was to characterize tobacco use among Afghan refugees. A survey was developed and translated into Dari and Pashto and then disseminated using community-based participatory research methods. To date, 248 Afghan adults (of the 400 Afghan adults resettled in Oklahoma City) have completed the survey. A total of 65.3% of the sample completed the survey in Pashto, 27.4% in Dari, and 7.3% in English. Participants were 58.9% male, with a mean age of 32 years (SD=9.4; range=18-61 years), and 71.8% were married. Overall, 12.1% of the sample used any type of tobacco, (19.9% of males, 1% of females). Cigarette smoking was the most commonly used form of tobacco use (10.5% of the sample), followed by hookah and chewing tobacco (.8% of the sample for each). More males smoked than females (17.1%, n=25/146 vs. 1%, n=1/102). A total of 16.5% of respondents reported living with a current smoker (not including themselves). Participants who reported current smoking lived with an average of 5 children in their homes. The majority (71.9%) of the participants reported that they had been smoking for ten or more years. Importantly, 87.5% of those who reported smoking also reported wanting to stop smoking, on a scale of 1-6, (1 =I don't want to quit smoking, 6 = I really want to stop smoking and intend to in the next 3 months), participants who smoked rated their motivation to quit as 3.6 (equivalent to "I want to stop smoking but don't know when I will"), (SD= 1.3). Tobacco users and non-users were compared by sociodemographic characteristics, age, sex, preferred language, education, income, partner status, and ethnicity. Only current monthly family income was associated with smoking, those who smoked had significantly higher income, earning on average $1,501-2,001 US dollars per month, compared to $1,000-1,500. Overall, we find that smoking rates among Afghan men are nearly double the national rate in the U.S., which impacts not only their health but the health of those who live with them. Efforts are needed to promote tobacco cessation among Afghan men resettled in the U.S.

INFLUENCE MDR (MULTIDRUG RESISTANCE) AND CELL-CELL INTERACTIONS ON DRUG UPTAKE OF SPHEROIDS

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Introduction: One of the major reasons for cancer treatment failure is relapse. Cancer relapse can occur due to drug resistance, a complex process that can be developed through various mechanisms. MDR plays a significant role in the development of drug resistance. Growing evidence indicates that MDR is regulated by increased efflux of anticancer drugs, resulting in reduced drug uptake by cancer cells. 2D-culture monolayer cancer cells are a popular model for studying cancers but are inefficient for understanding cell-cell interactions and microenvironments of in vivo tumors. In contrast, 3D-culture multicellular tumor spheroids (hereinafter referred to as spheroids) are more practical for studying cancers because spheroids play important roles in metastatic spread and chemoresistance.
Our previous studies of 2D co-culture models show that cell-cell interactions between drug-resistant and drug-sensitive cells can significantly increase the drug resistance level of the latter one. However, relevant studies in a 3D environment have not been carried out. The primary goal of the current study is to measure drug uptake in mono-cultured and co-cultured spheroids produced using drug-sensitive and drug-resistant cancer cell lines.

Experiments: Drug-resistant cell preparation. Regular HCT116 colorectal cancer cells were used as the drug-sensitive cells. HCT116 cells were treated with irinotecan (a common drug for colorectal cancer treatment to establish HCT116 drug-resistant cells, mimicking the induced drug resistance at the early-stage of chemotherapy.
Spheroid culture, drug treatment, and drug uptake measurement. In our studies of mono-cultured spheroids, both drug-sensitive and drug-resistant HCT-116 cell lines were used to culture two different types of spheroids. The co-cultured spheroids were produced using both cell lines. Spheroids were treated using paclitaxel for different time lengths, rinsed using FBS-free culture medium, and spheroid size was measured. We lysed spheroids, added the internal standard (i.e., deuterated paclitaxel) in the lysates, and measured the total amount of proteins in each lysed spheroid. We then conducted protein precipitation, desalting, and use nanoLC-MS measurements to quantify drug compound and its internal standard. Based on our experimental measurements, we determined drug amount and concentration in each spheroid. The protein amount was also used to normalize drug amount in each spheroid, allowing for a comparison of the relative drug abundances among all spheroids from different experiment conditions.

Future Studies: We will conduct similar studies using regular OVCAR-8 and drug-resistant cancer cell lines. Spheroids will be treated with traditional drugs (e.g., paclitaxel) and novel anticancer drugs (e.g., OSW-1). We will determine the drug uptake difference between paclitaxel and OSW-1 in spheroids with and without drug-resistant cancer cells.

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EFFECT OF STAT3 INHIBITORS, TTI-101 AND SH5-07, AGAINST BLADDER CANCER IN PRECLINICAL 3D TUMOR MODELS

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Bladder cancer (BC) is a lethal genitourinary malignancy associated with frequent recurrence and poor survival due to metastatic potential. Identification of key cancer cell signaling networks and developing promising agents is critical for effectively inhibiting tumor growth and progression. In many cancers, including bladder cancer (BC), signal transducer and activator of transcription 3 (STAT3) has emerged as an important molecular pathway due to its role in promoting proliferation, invasion, and chemoresistance. Thus, developing STAT3 targeting, orally bioavailable small molecule inhibitors may be helpful for the prevention of BC progression and improving the survival rate of patients with muscle invasive BC. Monolayer culture has limitations for drug testing. Therefore, spheroid and organoid culture are used extensively as they may mimic in-vivo drug response more accurately. The aim of our study is to examine the preclinical anticancer efficacy of STAT3 inhibitors [TTI-101 (C188-9) and SH5-07] in 3D (spheroid and tumoroid) invitro models of BC. We optimized the spheroid growth using various BC cell lines [human (J82), rat (NBT-II), and mouse (MB49) BC cells]. Similarly, tumoroids from rat (BBN-induced bladder tumors) and transgenic mice (UPII-SV40T) bladder tumors were developed. These spheroids and tumoroids were treated with various concentrations (0 - 50 µM range) of STAT3 inhibitors and evaluated for their viability [Calcein AM (CA) and EtBr staining], ATP production (CellTiter-Glo™ 3D), and ROS production (MitoSOX™). Effect of drug treatment on biomarkers of cell proliferation, apoptosis, stemness, STAT3 signaling, and immune modulation was determined using western blotting and immunofluorescence. Treatment with TTI-101 (0 - 50 µM or SH5-07 (0 - 50 µM) for 144 hrs resulted in significant reduction in the spheroids size (39-45% smaller Vs untreated; $p<0.0001$), along with decreased ATP levels (20%-40%, $p<0.05$). MitoSOX™ staining suggested that STAT3 inhibitors treatment increased ROS production in BC cells. CA and EtBr staining revealed that TTI-101 and SH5-07 treatment resulted in increased cell death in BC spheroids compared to control. Decreased spheroids and organoids size also correlated with increased apoptotic marker (cleaved caspase-3) along with decreased cyclin D1, PCNA, and pSTAT3 protein expression. Drug treated BC spheroids/tumoroids also showed reduction in CD44 (BC stemness and invasion marker) and induction of cGAS-STING pathway (cGAS, STING, TBK1, and IRF3) in comparison to the control. These findings indicate that STAT3

inhibitors, TTI-101 and SH5-07, could inhibit bladder cancer by suppressing STAT3 pathway activation and therefore warrant further study in vivo. (Supported by P30 CA225520 and Kerley-Cade Endowed Chair)

SITE SPECIFIC SERINE PHOSPHORYLATION OF PML PROTEIN IS ESSENTIAL FOR NEUROBLASTOMA DISEASE PROGRESSION AND METASTASIS

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Promyelocytic leukemia (PML) protein is the core component of the PML nuclear bodies (PML-NBs) and, a well-regarded tumor suppressor in many cancers including neuroblastoma. Stability of PML is crucial for the PML-NBs formation and, is governed by its phosphorylation in many serine residues. Crucially, PML phosphorylation at S^{518} is known to dictate PML poly-ubiquitination and degradation. Despite that undifferentiated neuroblastomas lack PML-NBs; and clinical strategies reinstating PML-NBs induced cellular differentiation; it is unclear how PML is destabilized in NB and its function in disease progression. Here, we investigated the intensity and function of PML phosphorylation at S^{518} in neuroblastoma evolution. Phosphorylation at S^{518} was significant in cell-lines (*n*=12) derived from patients with resistant progressive disease (PD, *vs.* those derived during Dx) and in metastasis site derived aggressive cells (MSDACs, *n=6*) from mouse models of PD (*vs.* cell lines from primary tumors, PXCs). Site-specific mutation (Quickchange II site directed mutagenesis) alternating serine residue at 518 with inhibiting (S-A) or continuously phosphorylating (S-E) residue, confirmed with sequence analysis and validated with immunoblotting. S-A mutated PD cells or MSDACs and S-E mutated Dx cells or PXCs unveiled site specific PML phosphorylation dependent regulation of neuroblastoma cell migration, invasion, and anchorage independent growth. Two independent mouse models with xenotransplantation of S-A and S-E mutated patient derived cells displayed the requirement of PML site (S^{518}) specific phosphorylation in tumor progression and metastasis. Together, these results demonstrate that phosphorylation of PML at S^{518} is essential for neuroblastoma evolution. Defining the mechanism(s) and the driver for S^{518} phosphorylation would allow us to develop new and improved molecular targeted therapy for progressive neuroblastoma.

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SMOKING TREATMENT HISTORY AND PREFERENCES AMONG ADULTS ENTERING A SMOKING CESSATION PROGRAM

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Background: Smoking is the leading cause of cancer and cancer deaths, and is a significant leading factor in health disparities associated with cancer. There are many validated resources that can be used to support a smoking cessation attempt (e.g., medications, state helplines). Previous smoking cessation experiences likely influence preferences for future quit attempts. This study examined resources used during past quit attempts, perceived effectiveness of smoking cessation medications, and preferences for future smoking cessation attempts.

Methods: Secondary analyses of data from a 13-week, 3-arm randomized controlled trial that tested a novel smoking cessation smartphone application were conducted for this study. Participants provided demographic information and answered questions about previously used smoking cessation resources and preferences for resources that they would like to use in future quit attempts.

Results: Participants (N=81) were female (50.6%), White (71.6%), 49 years old on average, and reported using the following to help them quit in the past: Chantix/Varenicline (34.6%), Zyban/Wellbutrin (23.5%), nicotine patch (63%), nicotine gum or lozenge or nasal spray (38.3%), other medication (3.7%), E-cigarettes (28.4%), quitline (18.5%), and smartphone app (1.2.%). A total of 21% of participants reported that they had not previously used any of the mentioned cessation tools. Of those that reported previous use of smoking cessation medications, 49.4% found the medications to be helpful and most participants (98.8%) reported that they would like to use smoking cessation medications to help them quit in the future. Further, in a forced single choice question of most preferred smoking cessation resource, participants reported that they would prefer to use medications (60.5%), in person individual

counseling (14.8%), smartphone app (8.6%), group counseling (4.9%), helpline phone counseling (4.9%), and no smoking cessation resources (6.2%).
Conclusion: Results indicated considerable variation in previous smoking cessation resource use and future cessation resource use preferences. Interestingly, nearly all participants reported that they would like to use smoking cessation medications in future quit attempts. Past smoking cessation experiences and future preferences for smoking cessation resources should be considered when treatment plans are developed for smokers that are attempting to quit. More research is needed to determine efficacy of smoking cessation treatments centered on smoker's preferences versus standard care.
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NEURAL CREST CELL (NCC) SPECIFIC KNOCKOUT OF RD3 DICTATED PREMALIGNANT MIRNA FOOTPRINT IN NCC DERIVED ADRENAL GLAND, BROWN ADIPOSE TISSUE AND SPINAL CORD

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Unwarranted genetic and molecular reprogramming in the neural crest cells (NCCs) during early stages of development divert the sympathoadrenal lineage and drive the genesis of neuroblastoma (NB). Our recent studies documented a significant loss of Retinal degeneration protein 3 (RD3) and demonstrated that RD3 loss not only associates with poor clinical outcomes but also functionally drives the NB pathogenesis. However, it is unclear whether the acquired loss of RD3 in embryonic NCCs is by itself a risk-factor for NB genesis. Here, we investigated whether NCC-specific knockout (KO) of RD3 sets the stage for NB genesis in NCC-derived tissues. We generated a unique transgenic mouse with Cre-conditional KO of RD3 in Tyrosine hydroxylase (active promoter in migrating NCCs in early development) expressing NCCs, termed TH-RD3-KO. RD3-loss driven modifications in miRNA landscape, if any, in NCC derived adrenal gland (AD), spinal cord (SC) and brown adipose tissue (BAT) was investigated in RD3-KO mice and compared to wild type mice (n = 4/group) using Nanostring ncounter whole miRNome expression assay and analyzed with integrated nSolver software. Differential expression analysis coupled with false discovery rate (log_{10}Padj) calculation clearly identified tissue specific miR modifications in NCC derived tissues (AD, 7up, 8 down; BAT, 2 up, 6 down; SC, 1up and 26 down). No single miR modification (up/down) displayed tissue independent regulation. Interestingly, miR-Walk bio-informatic analysis identified a tight interaction of these tissue specific miRs in regulating key molecular pathways (16 pathways common with upregulated miRs across tissues and 10 pathways with downregulated miRs) those regulate cellular proliferation, differentiation, migration, EMT, stemness maintenance). Together, the results demonstrate that NCC-specific RD3 KO instigates molecular rearrangements in NCC-derived tissues and prompts a pre-malignant niche. Uniquely, our data unveiled a tissue specific miRs rearrangement with RD3-KO in NCCs, yet all converge and orchestrate a common cause effect, the formation of pre-cancerous niche. The outcomes indicate RD3-loss in NCC during early development may serve as a risk factor for the genesis of NB.
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DIABETES AFTER BREAST CANCER TREATMENT: A ROLE FOR ADIPOCYTE PROGENITOR CELLS

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Breast cancer survivors have an elevated risk for type 2 diabetes compared to women who did not have cancer. Most (>75%) breast tumors are estrogen receptor (ER) positive, and patients are treated with endocrine therapies to block ER or that reduce estrogens. One study estimated that, of all the women to develop diabetes after breast cancer, 48% of the diagnoses were attributable to the treatment they received, particularly for the ER antagonist, tamoxifen. Diabetes can result from ectopic lipid deposition due to unhealthy adipose tissue expansion during weight gain, where the mature cells grow by hypertrophy without hyperplasia of the progenitor cells. In mice we showed that endocrine therapies promoted weight gain, impaired glucose tolerance, and worsened hepatic steatosis, associated with adipocyte hypertrophy and a depletion of adipose progenitor cells. Single cell RNA sequencing revealed a loss of the Wnt1-inducible signaling protein 2 (*Wisp2*) in progenitor populations from adipose tissue after endocrine therapy. Wisp2 promotes adipose stromal cell proliferation and contributes to metabolic health. We hypothesized that ER maintains adipocyte progenitor cells through induction of *Wisp2*. Here, we used mouse adipocyte precursor cells, which include the self-renewing progenitors and the committed preadipocytes and found that the *Esr1* and *Wisp2* genes were high in undifferentiated cells. *Esr1* was notably higher in progenitors than preadipocytes, and estrogen treatment induced *Wisp2* mRNA and protein expression, which was dependent upon ER. Flow cytometry showed that treatment with either estrogen or Wisp2 increased progenitor cells, while inhibition of ER with tamoxifen depleted them and instead increased preadipocytes. In summary, estrogen may regulate the balance between hypertrophy and hyperplasia, potentially through Wisp2. The results of this study may help us better understand and prevent the risk for diabetes in breast cancer survivors.

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DO SMOKERS INITIALLY UNMOTIVATED TO QUIT OPEN SMARTPHONE MESSAGES THAT PROMOTE AND SUPPORT SMOKING CESSATION ATTEMPTS?

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Smartphone-based ecological momentary assessment (EMA) can be used to identify predictors of cancer risk behaviors and inform tailored messaging that facilitate health behavior change. This study addresses a gap in the literature by identifying variables that predict viewing of prompted smartphone-based intervention messages across a long study period (>1 month).

Data for the present study come from a 3-group randomized controlled trial that enrolled adults (*N*=152) who were not ready to quit smoking cigarettes in the next 30 days. Participants were randomized into groups that received twice daily messages for 182 days, tailored to each participant's current smoking cessation stage (2 intervention groups) or were not related to smoking cessation (control group). Linear regression models tested the association between person-level aggregate messages viewed and predictors (i.e., group, age, gender, race, education, employment, rural/urban, mental health diagnosis). Growth models tested compliance across weeks in study and assessed predictors as moderators.

Participants were mostly White (73%), female (68%), unemployed (53%), urban residence (77%), and middle-aged (*M*=50.0 years, *SD*=12.5) with 13.3 years of education (*SD*=1.6). Across the sample, 31,503 messages were viewed across a total of 17,580 days. On average, participants viewed 61% of prompted messages. Age was the sole predictor of aggregate compliance since it was positively associated with total and morning message compliance (*p*=0.018 and 0.007), but not with evening message compliance (*p*=0.053). Weeks in study was associated with a decline in morning (*β*=-0.011, *p*<0.001), evening (*β*=-0.011 *p*<0.001) and total (*β*=-0.011 *p*<0.001) messages

viewed. Gender significantly interacted with weeks in the study, producing a more rapid reduction of compliance among males (v. females) for morning (β_M=-0.018; β_F=-0.008, p<0.001), evening (β_M=-0.017; β_F=-0.008, p<0.001) and total messages (β_M=-0.018; β_F=-0.008, p<0.001). Urban (v. rural) residence related to significantly faster decline of morning (β_{rur}=-0.008; β_{urb}=-0.012, p<0.001), total (β_{rur}=-0.009; β_{urb}=-0.012, p=0.002), but not evening messages. Being employed was also linked with accelerated decline in morning (β_{emp}=-0.013; β_{unemp}=-0.010, p=0.005), total (β_{emp}=-0.012; β_{unemp}=-0.010, p=0.028), but not evening message compliance. As years of education increased, slower was the decline in compliance for morning (est=0.001, p=0.002), evening (est=0.002, p<0.001), and total messages (est=0.001, p<0.001).

Surprisingly, age was the only significant predictor related to overall number of intervention messages viewed. The number of messages viewed progressively decreased across the 6-month study period, but the rate of decline varied across predictor variables. Since tailored messages facilitate health behavior change, longer duration EMA interventions should identify ways to maintain high levels of message viewing across time and participant characteristics.

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DAILY CANNABIS USE AND DEMOGRAPHICS INTERACT TO EFFECT AFFECT AND OTHER SUBSTANCE USE

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Background: As cannabis use becomes more prevalent, researchers are increasingly examining the consequences of its use. Ecological momentary assessment (EMA) has enabled researchers to examine the contextual factors, predictors, and proximal effects of cannabis at a granular level. The present study used EMA data to examine the effects of cannabis use on next day stress, happiness, and alcohol and cigarette use.

Methods: Daily EMA data from a nationwide randomized controlled trial examining factors related to EMA compliance (N=456) were used for this sub-study. Participants received 2-4 daily EMAs for 28-days. Those who reported using cannabis at least once during the EMA period were included in the analyses (n=96). During the morning EMA, participants were asked about cannabis, alcohol, and cigarette use "yesterday." During each EMA (2-4 per day) participants were also asked about their current level of happiness and stress using two different scales (i.e., for 14 days a slider-type scale from 0 (None) to 10 (High) was used and for 14 days a 5-point Likert-type scale was used (from 1 = Strongly Disagree to 5 = Strongly Agree). Affect items were aggregated separately by day for the current analyses. Multilevel analyses were conducted to examine relationships between yesterday's cannabis use and today's happiness, and stress; and multilevel time lag analyses were used to study the effect of yesterday's cannabis use on today's alcohol use and tobacco use. Covariates (i.e., age, race, sex) were added into the analysis.

Results: Participants (n=96) were on average 46.5 years old (SD=12.3), mostly White (69%) and female (71%) and reported using cannabis on 12.0 days (SD=9.0; range: 1-28 days). Prior day cannabis use was not related to stress on the next day. However, cannabis use days were related to lower levels of next day happiness on slider-type ($p<0.05$), but not Likert-type questions. Results indicated that on days when cannabis was used, non-White participants consumed more alcohol the next day compared with White participants, $p<0.05$. Furthermore, using cannabis was related to a greater increase in cigarettes smoked the next day for women compared with men, $p<0.05$.

Conclusion: Cannabis use may be associated with lower next-day happiness. In addition, demographic variables (e.g., race and sex) may interact with cannabis use to influence next day alcohol and cigarette use. More research is needed to examine mechanisms for these relationships.

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ASSOCIATION OF FINANCIAL STRAIN WITH TOBACCO USE CHARACTERISTICS AMONG SOCIOECONOMICALLY DISADVANTAGED ADULTS PARTICIPATING IN SMOKING CESSATION TREATMENT

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Smoking rates among socioeconomically disadvantaged adults are much higher than in the general population, and socioeconomic disadvantage is associated with a return to smoking during a smoking cessation attempt. Financial strain (FS) refers to difficulty or inability to afford basic necessities and comforts, and has been linked to tobacco use characteristics including cigarettes smoked per day and dependence, as well as depression and negative affect in current smokers. The goal of the present study was to evaluate the association of FS with tobacco use characteristics and smoking cessation among socioeconomically disadvantaged adults.

Participants were uninsured or Medicaid-insured adults (M_{age}=48.9 years, 63.1% female, 60.6% NH White; *N*=320) and randomized to receive either standard care (SC; *n*=161) or SC plus financial incentives (*n*=159) in a smoking cessation program. They reported demographics, FS, tobacco use characteristics, and mental health at baseline. Abstinence was biochemically-confirmed at weeks 1-4, 8, 12, and 26. Adjusted linear regression models examined associations of FS and average cigarettes smoked per day, years of smoking, Intolerance for Smoking Abstinence Discomfort Questionnaire (ISADQ), Heaviness of Smoking Index (HSI), Brief Questionnaire of Smoking Urges (QSU), Wisconsin Smoking Withdrawal Scale (WSWS), Center for Epidemiological Studies Depression (CES-D), and the negative affect (NA) subscale of the Positive and Negative Affect Schedule at baseline. (covarying treatment group, HSI, race, sex, age, and education). Adjusted logistic regression models examined FS as a predictor of abstinence at each follow-up (same covariates as above).

In adjusted linear regression models, FS was significantly associated with ISADQ scores (*B*=.25, *p*=.002), HSI (*B*=.03, *p*=.001), QSU (pos. reinforcement: *B*=.15, *p*=.031; neg. reinforcement: *B*=.20, *p*=.004), CES-D (*B*=.50, *p*<.001), and NA (*B*=.35, *p*<.001) at baseline. FS was not associated with average cigarettes per day, years of smoking, or WSWS at baseline. In adjusted logistic regression models, FS at baseline did not predict abstinence at any follow-up, except week 2.

While baseline FS was not predictive of abstinence at most follow-ups, FS was associated with tobacco-related characteristics and negative emotions at the beginning of a quit attempt. Findings suggest that adults with greater FS may experience more discomfort during a smoking cessation attempt, which may be addressable through targeted counseling approaches and pharmacotherapies.

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POLYAMINES ARE POSITIVE REGULATORS OF GROUP 3 INNATE LYMPHOCYTE ACTIVATION

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Group 3 innate lymphocytes (ILC3s) are rare, tissue resident immune cells. They respond to innate inflammatory signals, such as the cytokine IL-23, that are induced by pathogens or cancer. Upon activation immune cells must rapidly alter their metabolism to meet the energy demands for proliferation and function, which includes production of effector proteins and cytokines. Metabolic adaptations regulating ILC3 activation are not completely understood. Polyamines are polycationic metabolites that have diverse roles in cellular functions and in immunity regulate immune cell biology, including Th17 cells, which are the adaptive immune counterpart of ILC3s. Whether polyamines play a role in ILC3 activation is unknown. Here we report that the polyamine synthesis pathway is important for ILC3 activation. IL-23-activated mouse ILC3s upregulate ornithine decarboxylase (ODC), the enzyme catalyzing the rate-limiting step of the conversion of ornithine to putrescine in polyamine synthesis, with a subsequent increase in putrescine levels. Inhibition of ODC via a specific inhibitor, α-difluoromethylornithine (DFMO), reduced levels of activation-associated cytokines produced by steady-state or IL-23-activated ILC3s in a putrescine-dependent manner. Thus, the polyamine putrescine is a positive regulator of ILC3 activation. Our results suggest that polyamines represent a potential target for therapeutic modulation of ILC3 activation during infection or cancer.

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ACETYL-COA SYNTHETASE 2 PROMOTES MACROPINOCYTOSIS AND CANCER CACHEXIA IN PANCREATIC CANCER

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Background: Nutrient deficiency and cachexia are two hallmarks of pancreatic cancer. Acetyl-coA Synthetase 2 (ACSS2) is upregulated in nutrient deficient condition in several cancer types, such as glioblastoma and breast cancer. But its role in pancreatic cancer remains poorly understood. Macropinocytosis is a non-selective protein scavenge process crucial for amino acids supply. This study aims to investigate how ACSS2 mediates metabolic reprogramming to drive macropinocytosis and cachexia in pancreatic cancer.

Methods: ACSS2 knockout or overexpression human pancreatic cancer cell lines and ACSS2 knockdown KPC cell line were established. Macropinocytosis level was evaluated by dextran uptake assay. Cell proliferation was determined by spheroids, EdU and MTT assay. ChIP assay was performed to demonstrate transcriptional activation of ETV4 and CREB. Orthotopic pancreatic cancer mouse model was established to evaluate the role of ACSS2 *in vivo*. Muscle wasting was examined in mouse muscle tissue and C2C12 myotubes.

Results: Nutrient deficiency upregulates ACSS2, which is associated with worse overall survival in pancreatic cancer. ACSS2 promotes cell proliferation and macropinocytosis. Nutrient deficiency upregulates macropinocytosis associated genes SDC1 and DNM2 through ZIP4. Knockdown of ZIP4 reverses ACSS2 induced macropinocytosis and cell proliferation. ACSS2 regulates ZIP4 through ETV4, which binds to the promoter region of ZIP4. ZIP4 promotes macropinocytosis through CREB mediated SDC1/DNM2 pathway. Meanwhile, ACSS2/ZIP4 promotes muscle wasting via GSK3β/TRAIL signaling axis. Knockout of ACSS2 reverses cachexia and improves overall survival in orthotopic mouse model of pancreatic cancer.

Conclusion: ACSS2 regulates metabolic reprogramming through ETV4/ZIP4 pathway, which promotes macropinocytosis via SDC1/DNM2 and drives muscle wasting via GSK3β/TRAIL in pancreatic cancer.

Conflict of Interest: The authors declare that they have no conflict of interest.

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