48th Annual UNC Lineberger Comprehensive Cancer Center
Postdoctoral-Faculty Research Day

Thursday October 5th, 2023, 7:45am-6:00pm
Carolina Inn – Hill Ballroom & Chancellors Ballroom
211 Pittsboro St, Chapel Hill, NC 27516

This event is sponsored by the UNC Lineberger Comprehensive Cancer Center - Cancer Research Training and Education Coordination (CRTEC).

Planning and implementation of this event was made possible by the essential support of Dr. Shelley Earp, the postdoctoral committee members, and by the generous assistance of LCCC faculty and staff.

Shelton "Shelley" Earp, MD

Lineberger Professor of Cancer Research
Director, UNC Lineberger Comprehensive Cancer Center
Director, UNC Cancer Care

Postdoctoral Committee Members

Kenneth Busby III, DO

Zhenzhen Chen, PhD

Victoria Dunsmore, PhD

Kristina Drizyte-Miller, PhD

Ilona Fridman, PhD

Denis Okumu, PhD

Faculty Advisor

Bernard E. Weissman, PhD
Professor of Pathology and Laboratory Medicine, LCCC Associate Co-Director of Education

CRTEC Staff

Becca Moss, Lisa Meadows, Julie Trollinger, Barbara Austin

7:45-8:45am
Breakfast
Chancellors Ballroom

8:45-9:00am
Welcome Remarks
Hill Ballroom - Central & South, Zoom Session A

Shelton "Shelley" Earp, MD
Lineberger Professor of Cancer Research
Director, UNC Lineberger Comprehensive Cancer Center
Director, UNC Cancer Care

9:00-10:45am
Honored Alumni Speakers
Hill Ballroom - Central & South, Zoom Session A

Introduction: Adrienne Cox, PhD, Pharmacology

9:00-9:50 **Aaron Hobbs, PhD**
Assistant Professor, Department of Cell and Molecular Pharmacology & Experimental Therapeutics
Medical University of South Carolina
KRAS mutant-selective signaling in pancreatic cancer: Defining your own research program in the shadow of giants

Introduction: Jennifer Lund, PhD, Epidemiology

9:55-10:45 **Emilie Duchesneau, PhD**
Assistant Professor, Department of Epidemiology and Prevention**,** Wake Forest University - School of Medicine
Patient-centered cancer outcomes research: Moving beyond mortality

10:45-11:15am
Coffee Break
Colonnade

11:15am-12:00pm
Session 1 (A): Basic & Clinical/Translational Sciences
Hill Ballroom - Central & South, Zoom Session A
Chair: Denis Okumu, PhD

11:15-11:35 **Wen-Hsuan Chang, PhD**
Postdoc, LCCC, Channing Der Lab, Clinical or Translational Research
Title: KEAP1-NRF2-mediated resistance against $KRAS^{G12D}$ inhibitor in pancreatic cancer
Authors: Wen-Hsuan Chang[1], Andrew M. Waters[1,4], Kirsten L. Bryant[1,2], Adrienne D. Cox[1,2,3], Channing J. Der[1,2]
1- Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599
2- Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599
3- Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599
4- Department of Cancer Biology, University of Cincinnati, Cincinnati, OH 45267

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer deaths in the US. Mutational activation of the KRAS oncogene is associated with 95% of PDAC and is essential for maintaining PDAC tumorigenic growth. Although inhibitors (sotorasib and adagrasib) targeting one KRAS mutation (glycine-12 to cysteine; G12C) have been approved for the treatment of $KRAS^{G12C}$-mutant lung cancers, the G12C mutation comprises less than 2% of KRAS mutations in PDAC. Recently, the clinical candidate KRAS inhibitor MRTX1133 (G12Di) has been shown to be selective for the G12D mutation and to potently suppress the tumorigenic growth of $KRAS^{G12D}$-mutant PDAC in vivo. Since $KRAS^{G12D}$ comprises 40% of KRAS-mutant PDAC, G12D-targeted inhibitors hold promise as an effective therapy for a significant fraction of PDAC patients. However, the potential of these inhibitors is hindered by persistent challenges related to both primary (innate) and acquired treatment-associated resistance, which curtails the long-term effectiveness of G12C-specific and likely other KRAS inhibitors. Here, our studies are focused on unraveling primary and acquired mechanisms that drive PDAC resistance to G12Di treatment. Applying CRISPR loss-of-function screens on PDAC cells treated with G12Di, we found that knockout of *KEAP1* compromised the ability of G12Di to inhibit PDAC cell proliferation in vitro. KEAP1 is a substrate-specific adapter of an E3 ubiquitin ligase complex. KEAP1 loss is associated with increased expression of the KEAP1 substrate, NRF2, resulting from decreased protein degradation. The NRF2 transcription factor is a master regulator of anti-oxidative stress responses. Interestingly, we determined that the G12Di-resistant KEAP1-deficient PDAC cells exhibited increased dependence on glutaminase, which converts glutamine to glutamate. Thus, we are currently investigating the effectiveness of combining a glutaminase inhibitor (CB-839) with G12Di to overcome KEAP1 loss-mediated resistance. In summary, our study establishes a role for KEAP1 loss as a mechanism that drives PDAC resistance to KRAS inhibitors and identifies glutaminase inhibition as a possible approach to overcome NRF2-driven resistance.

11:35-11:55 **Hannah Trembath, MD**

Postdoc, Surgery, Dr. Jen Jen Yeh, UNC Integrated Translational Oncology Program, Basic Science

Title: Does Presence Of New Onset Diabetes Predict Pancreatic Adenocarcinoma Subtype?

Authors: Hannah Trembath, Joseph Kearney, Jen Jen Yeh

Abstract:

Introduction: Pancreatic adenocarcinoma (PDAC) is an extremely lethal disease with dismal long term survival. The relationship between diabetes mellitus (DM) and PDAC is multifaceted and better understanding it is a stated NIH research priority. DM is a known PDAC risk factor; there is a subset of PDAC patients with new onset DM (NOD), who are diagnosed with PDAC <2 years after DM diagnosis that is currently under investigation regarding the pathophysiology, demographics, outcomes, as well as a potential group to screen.

There are two molecular subtypes of PDAC, basal and classical, that are prognostic and predictive of chemotherapy response. While subtyping assays have been developed, they are not yet utilized for majority of PDAC patients. We set out to evaluate if presence of NOD correlates with molecular subtype and could be used as a subtype proxy to help guide prognosis and treatment decisions.

Methods: This is a single institution, cohort study using retrospective review of hospital data and RNA sequencing data. To be included in the study, patients had to have PDAC on pathology specimen review, RNA sequencing data from resected specimen for molecular subtyping, and have undergone resection from 2009-2022. Demographic and clinical factors were examined using bivariate and multivariate analysis.

Results: We identified 139 patients that met inclusion criteria: 84 patients with no history of DM, 31 patients with longstanding DM (>2 years), 16 with NOD, and 8 patients with a missing date of DM diagnosis and were thus excluded from the analysis. There were 120 patients with classical subtype and 11 with basal subtype. The demographics between groups were overall similar, however BMI was higher in the group of longstanding DM compared to no DM (M=29.1 SD=5.4, M=25.8, SD=4.8), but not statistically different from NOD. After controlling for age, sex, race, and preoperative weight, NOD was not a significant predictor of PDAC subtype (OR 0.62, 95% CI 0.06, 6.1). Increasing age was associated with slightly decreased odds of having basal subtype (OR 0.91, 95% CI 0.85, 0.98, p value 0.02).

Conclusion: As continued interest in the NOD PDAC patient group mounts, we sought to see if NOD could be used in subtype prediction and hence, aid in prognosis and treatment choices. We are the first to our knowledge, to show that NOD and PDAC subtype are not associated and NOD cannot be used to predict PDAC subtype at this time. Additionally, we found that sex, race, and preoperative weight are poor predictors of subtype. However, there

could be different demographic or clinical factors that may be identified in the future to aid in subtype predication. Further investigation into underlying pathophysiology of the NOD group is still needed.

11:15am-12:00pm

Session 1 (B): Population Sciences

11:15-12:00pm, Hill Ballroom - North, Zoom Session B

Chair: Victoria Dunsmore, PhD

11:15-11:30 **Ilona Fridman, PhD**

Postdoc, LCCC, Jennifer Elston Lafata, Cancer Care Quality Training Program, Population Science - Public Health

Title: Preferences for electronic modes of communication among older primary care patients: a cross-sectional survey

Authors: Ilona Fridman, Ahmaya Smalls, Patrice Fleming, Jennifer Elston Lafata

Objective: Health information delivered via daily modes of communication such as email, text, or telephone has been shown to support improved health behavior and outcomes. While different modes of communication beyond clinical visits have proven successful for patient outcomes, preferences for communication modes have not been comprehensively studied among older primary care patients. We addressed this gap by assessing patient preferences for receiving cancer screening and other information from their doctor's office. We explored stated preferences by communication modes through the lens of social determinants of health (SDOH) to gauge acceptability and equity implications for future interventions.

Methods: A cross-sectional survey was mailed to primary care patients aged 45-75 years, in 2020-21. The survey assessed respondents' use of telephones, computers, or tablets in daily life and their preferred modes of communication for different types of health information, including educational materials about cancer screening, tips for taking prescription medication, and protection from respiratory diseases from their doctor's office. Respondents indicated their willingness to receive messages from their doctor's office via each of the provided modes of communication, including telephone, text, email, online patient portal, website, and social media. They reported on a 5-point Likert scale that ranged from "unwilling" to "willing." We present the percentage of respondents who indicated that they were "willing" to receive information via specific electronic mode. Chi-square tests were used to compare participants' willingness by social characteristics.

Results: In total, 133 people completed the survey with a response rate of 27%. The average age of respondents was 64 years; 63% of respondents were female; 83% were White, 16% were Black, and 1% were Asian. In total, 58% reported having a bachelor's degree or higher; 20% resided in rural areas, 29% in suburban areas, 39% in a town, and 12% in a city. The majority, 57%, reported being comfortable with their income. Preferences of respondents for electronic communication about cancer screening were distributed as follows: 75% of respondents were willing to receive information from their doctor's office via their patient portal, 74% via email, 56% via text, 45% via the hospital website, 38% via telephone, and 11% via social media. About 5% of respondents were unwilling to receive any communication by electronic mode. Preferences were distributed similarly for other types of information. Respondents reporting less income and less education consistently preferred receiving telephone calls relative to other communication modes.

Conclusions: To optimize health communication and reach a socioeconomically diverse population, telephone calls should be added to electronic communication, especially for people with less income and education. Further research needs to identify the underlying reasons for the observed differences and how best to ensure that socioeconomically diverse groups of older adults can access reliable health information and healthcare services.

11:30-11:45 **Sarah Asad, PhD Candidate, MSc**

2023 Marci K. Campbell Dissertation Award

Graduate Student, Health Policy and Management, Dr. Sarah Birken and Dr. Erin Kent, Cancer Care Quality Training Program, Population Science - Public Health

Title: Unboxing the endometrial cancer diagnostic pathway: Multilevel determinants of timely diagnosis of endometrial cancer as experienced by Black women with endometrial cancer and clinicians who refer them.

Background: In the United States, endometrial cancer (EC) affects 1 in 37 women with incidence rates continuing to climb. Incidence of EC is higher in White women, and yet EC mortality rates are 80% higher in Black women. Studies suggest disparities in outcomes are associated with patient-level characteristics (e.g., access to care), but less is known about informational and communication factors in Black women's diagnosis experience of EC. Guideline-concordant diagnosis of EC may be influenced by patient-provider communication through determinants at levels beyond the individual level. To date, there is limited knowledge and understanding of multi-level determinants (e.g., individual, community, and health care system) that impact patient-provider communication as patients move in the diagnostic pathway to obtain a timely diagnosis of EC.
Objective: This study identifies multi-level determinants of patient-provider communication influencing EC diagnosis to inform the development of a system-strengthening intervention to improve timely diagnosis.
Methods: This study uses qualitative semi-structured interviews with Black women with a diagnosis of EC, and clinicians who were in the position to refer or diagnose EC. Interviews were guided by the socio-cultural framework for the study of health service disparities (SCF-HSD). Interviews were coded using deductive thematic analysis using codes from the SCF-HSD framework, and inductive thematic analysis for new themes arising in the data. Patients were recruited from an online research platform 'Research for Me' at University of North Carolina at Chapel Hill from May to July 2022. Eligible patients had to identify as Black, English-speaking, aged 40 years or older, and have a diagnosis of EC within the last 3 years. Eligible clinicians recruited for this study were health care professionals who might be the first point of contact involved in caring for patients with reproductive tract symptoms. Clinicians were purposively recruited across the US using primary authors' professional network in North Carolina, and through snowballing.
Results: Twenty-two individuals chose to participate in online and phone interviews. Clinician interviews ranged from 12-27 minutes, and patient interviews between 21-53 minutes. Thirteen patient participants were primarily between 40-44 years of age, stage II (100%), and either had private (31%), Medicare (31%) or Medicaid (38%) health insurance. Nine clinician participants practiced within a variety of clinical settings and roles (e.g., primary care physician, nurse practitioner, physician's assistant, gynecologist, and hospitalist). There were 3 overarching themes among both groups. Participants brought up the use of social networks to access care as patients and professional networks to provide referrals as clinicians, misunderstanding or disorientation of the EC diagnosis care sequence, and a lack of feeling comfortable with white health care providers as a Black woman seeking care.
Contribution and Significance: This study contributes to the understanding and investigation of multi-level determinants of EC diagnosis in Black women. Specifically, findings will point to critical determinants to patient-provider communication that may reduce disparity in access to timely diagnostic services for Black women. Findings of this study offer future researchers insight on the use of implementation science methods and frameworks to examine multilevel determinants of racial disparities and health inequities. The findings also offer policy makers insight on existing inequities in the diagnosis pathway of gynecological cancers and improvement of funding resources for accessing timely care.

11:45 – 12:00pm **Caitlin Biddell, PhD**
2023 Marci K. Campbell Dissertation Award
Researcher at Mathematica, Population Science Public Health
Title: Economic evaluation of a non-medical financial assistance program on missed oncology treatment appointments
Authors: Biddell CB, Spees LP, Trogdon JG, Kent EE, Rosenstein DL, Angove RSM, Rogers CD, Wheeler SB
Purpose: We retrospectively evaluated the clinical and economic impact of a program providing non-medical financial assistance on missed treatment appointments among patients receiving cancer treatment at a large, Southeastern public hospital system.
Methods: We used patient electronic health records, program records, and cancer registry data to examine the impact of the program on rates of missed (or "no-show") radiation therapy and infusion chemotherapy/immunotherapy appointments in the 180 days following treatment initiation. We employed propensity weighting to estimate the effect of the program, stratified by treatment appointment type (radiation therapy, infusion chemotherapy/immunotherapy). We developed a decision tree-based economic model to conduct a cost-consequence analysis from the health system perspective in a hypothetical cohort over a six-month time horizon.

Results: Of 1,347 patients receiving radiation therapy between 2015 and 2019, 53% (N=715) had ≥1 no-shows, and 28% (N=378) received program assistance. Receipt of any assistance was associated with a 2.1 percentage point (95% CI: 0.6 – 3.5) decrease in the proportion of no-shows, corresponding to a 51% decrease in the overall mean no-show proportion. Under the current funding model, the program is estimated to save the health system $153 per missed appointment averted, relative to not providing non-medical financial assistance. Of the 1,641 patients receiving infusion chemotherapy/immunotherapy, 33% (N=541) received program assistance, and only 14% (N=223) had ≥1 no-shows. The financial assistance program did not have a significant effect on no-show proportions among infusion visits.
Conclusion: This study employed a novel approach to retrospectively evaluate a non-medical financial assistance program for patients undergoing active cancer treatment. Findings support investment in programs that address patients' non-medical financial needs, particularly for those undergoing intensive radiation therapy.

12:00-1:00pm
Lunch
Chancellors Ballroom

1:00-2:00pm
Session 2 (A): Basic & Clinical/Translational Sciences
Hill Ballroom - Central & South, Zoom Session A
Chair: Denis Okumu, PhD & Kristina Drizyte-Miller, PhD

1:00-1:20 **Liu Mei, PhD**
2023 Joseph S. Pagano Award
Postdoc, Biochemistry and Biophysics, Jean Cook Lab, Basic Science
Title: The consequences of differential MCM loading dynamics in distinct chromatin environments
Abstract: Eukaryotic chromosomes contain regions of varying accessibility, yet DNA replication factors must access all regions. The first replication step is loading MCM complexes to license replication origins during the G1 cell cycle phase. It is not yet known how mammalian MCM complexes are adequately distributed to both euchromatin regions and heterochromatin regions. To address this question, quantify the relative rates of MCM loading in euchromatin and heterochromatin throughout G1. We found that MCM loading in euchromatin is faster than that in heterochromatin in early G1, but surprisingly, heterochromatin loading accelerates relative to euchromatin loading in middle and late G1. The different loading dynamics require ORCA-dependent differences in origin recognition complex distribution. A consequence of heterochromatin licensing dynamics is that cells experiencing a truncated G1 phase from premature cyclin E expression enter S phase with underlicensed heterochromatin, and DNA damage accumulates preferentially in heterochromatin in the subsequent S/G2 phase. Thus, G1 length is critical for sufficient MCM loading, particularly in heterochromatin, to ensure complete genome duplication and to maintain genome stability.

1:20-1:40 **Zhichuan Zhu, PhD**
2023 Joseph S. Pagano Award
Postdoc, Biochemistry and Biophysics, Pengda Liu, Basic Science
Title: STING Suppresses Mitochondrial VDAC2 to Govern Renel Cell Carcinoma Growth Independent of Innate Immunity
Authors: Zhichuan Zhu, Xin Zhou, Hongwei Du, Erica W. Cloer, Jiaming Zhang, Liu Mei, Ying Wang, Xianming Tan, Austin J. Hepperla, Jeremy M. Simon, Jeanette Gowen Cook, Michael B. Major, Gianpietro Dotti, and Pengda Liu
Abstract: STING is an innate immune sensor for immune surveillance of viral/bacterial infection and tumorigenesis. However, if and how STING exerts innate immunity-independent function remains elusive. Here, we report STING expression is increased in renal cell carcinoma (RCC) patients and governs tumor growth through non-canonical innate immune signaling involving homeostasis of mitochondrial calcium and ROS. We identify mitochondrial voltage dependent anion channel VDAC2 as a new STING binding partner. STING depletion potentiates VDAC2/GRP75-mediated mitochondria-ER contact to increase mitochondrial ROS/calcium levels, impairs

mitochondria function and suppresses mTORC1/S6K signaling leading to RCC growth retardation. STING interaction with VDAC2 occurs through STING-C88/C91 palmitoylation and inhibiting STING palmitoyl-transferases ZDHHCs by 2-BP significantly impedes RCC cell growth alone or in combination with first-line treatment sorafenib. Together, our studies reveal an innate immunity-independent function of STING in regulating mitochondrial function and growth in RCC, providing a rationale to target the STING/VDAC2 interaction in treating RCC.

1:40-2:00 **Sirui Li, PhD**
2023 Joseph S. Pagano Award
Postdoc, LCCC, Jenny Ting, Basic Science
Title: STING-induced B regulatory cells compromise NK function in cancer immunity
Authors: Sirui Li[1,2,3*], Bhalchandra Mirlekar[1,2*], Brandon M. Johnson[1,3] , W. June Brickey[1,3], John A. Wrobel[1,2,3], Na Yang[4], Dingka Song[3,+], Sarah Entwistle[1,5], Xianming Tan[1], Meng Deng[1,6], Ya Cui[7], Wei Li[7], Benjamin G. Vincent[1,5], Michael Gale, Jr.[8], Yuliya Pylayeva-Gupta[1,2#], Jenny P.-Y. Ting[1,2,3,6#]
Abstract: An immunosuppressive tumor microenvironment is a major obstacle in the control of pancreatic and other solid cancers. STING (stimulator of interferon genes) agonists trigger inflammatory innate immune responses to potentially overcome tumor immunosuppression. Although these agonists hold promise as potential cancer therapies, tumor resistance to STING monotherapy has emerged in clinical trials and the mechanism(s) are unclear. We show that the administration of five distinct STING agonists, including cGAMP, results in an expansion of human and mouse IL-35+ regulatory B lymphocytes in pancreatic cancer. Mechanistically, cGAMP drives B cell IL-35 expression in an IRF3-dependent but type I interferon-independent manner. In multiple preclinical cancer models, the loss of STING signaling in B cells increases tumor control. Furthermore, IL-35 blockade or genetic ablation of IL-35 in B cells also reduces tumor growth. Unexpectedly, the STING-IL-35 axis in B cells reduces NK proliferation and attenuates NK-driven anti-tumor response. These findings reveal an intrinsic barrier to systemic STING agonist monotherapy and provide a novel combinatorial strategy to overcome immunosuppression in tumors.

1:00-2:00pm
Session 2 (B): Population Sciences
Hill Ballroom - North, Zoom Session B
Chair: Ilona Fridman, PhD

1:00-1:20 **Victoria Dunsmore, PhD**
Postdoc, LCCC, Stephanie B. Wheeler, PhD, Population Science - Public Health
Title: Anticipatory Coping Diversity: Education Differences in the effects of Scanxiety
Authors: Dunsmore VJ, Neupert SD
Abstract: The days prior to a CT scan can be very stressful among lung cancer survivors (Bauml et al., 2016), and the feeling of scan-related anxiety during these days is so pervasive it has even been termed 'scanxiety' (Feiler, 2011). Anticipatory Coping (AC) involves targeted cognitive and behavioral efforts to prepare for a known upcoming stressor as it approaches (Feldman & Hayes, 2005), and in the context of recurrent scans, some AC strategies have been shown to be related to increases in scanxiety in the days before one's scan (Dunsmore & Neupert, 2022). Interestingly among the general population though, more diversity in AC strategies is related to better emotional reactivity to daily stressors, but those with more educational background tend to report less AC diversity (Neupert, 2022). Here, we extend this work to understand how education can moderate the relationship between scanxiety and AC diversity among a group of patients with lung cancer who are approaching their recurrent CT scan. 25 individuals (*M* age = 62.33, [*SD* = 8.10], 96% women, 80% white) participated in the study. Participants received a baseline demographics survey, and 8 consecutive daily surveys leading up to, as well as the day of, their scan asking about AC and daily scanxiety. 146 daily surveys were analyzed and AC diversity was indexed at the daily-level using Shannon's (1948) entropy. Consistent with past work, patients with a higher educational background reported lower levels of AC diversity (γ_{01} = -0.12, *t* = -5.02, *p* < .0001). An interaction was found between scanxiety and education such that among individuals with higher education, low scanxiety was related to lower AC diversity in the days prior to one's scan (γ_{11} = 0.03, *t* = 4.15, *p* < .0001). Individuals with low education reported high AC diversity, regardless of their scanxiety levels on a particular day. Future work should examine the mechanisms by which

education contributes to this disparity by class, as those with low education try to use more coping strategies, and therefore more mental resources, to alleviate daily scanxiety compared to those with high education.

1:20-1:40 **Alexander Ross Hurley, PhD, MPH**
Postdoc, Health Behavior, Deborah Tate, Carmina Valle, Cancer Health Disparities Training Program
Title: Content analysis of young adult cancer survivor peer conversations within a closed mHealth intervention social media group over 6 months
Authors: Lex Hurley, Ph.D., MPH, University of North Carolina at Chapel Hill, Department of Health Behavior Carmina G. Valle, Ph.D., MPH, University of North Carolina at Chapel Hill, Department of Nutrition, Lineberger Comprehensive Cancer Center
Background: Young adult cancer survivors (YACS) are an understudied population at increased risk for multiple chronic diseases. A majority do not adhere to recommended physical activity (PA) guidelines for survivors to lower risk of such morbidities, and few programs are specialized to meet this vulnerable population's unique needs. IMPACT was a 12-month randomized trial of an mHealth intervention designed to increase PA among YACS (N = 280) compared with a self-help group. The intervention group received adaptive goal setting, Fitbit activity trackers, tailored feedback, text messages, and up to 5 prompts each week posted into a private Facebook group by study staff to promote engagement. Conversely the self-help comparison group only received the Fitbit activity trackers and a separate private Facebook group which received minimal interaction by study staff. Over the course of the study, the self-help group displayed comparable levels of conversation activity on their Facebook wall relative to the moderated intervention group. This secondary analysis seeks to understand and document the types of peer-to-peer interactions among YACS within a closed Facebook group.
Methods: Facebook wall activity for both groups was manually recorded and coded by study staff weekly. This analysis used a subsample of the first 6 months (26 weeks) of post and comment data from approximately n = 78 participants on the basis that mHealth participation and engagement tends to decrease quickly after 6 months. This analysis represents a conventional content analysis using a constructivist epistemology, with a codebook iteratively developed over three waves of analysis to best ensure all content was appropriately identified among user posts and comments.
Results: Discussions mostly aligned with the focus of the study to enhance physical activity, with most conversations relating to social support, physical activity, Fitbits, and cancer specific topics. Participants were often forthcoming about sensitive health issues in their group introductions including diagnoses, chemotherapy, medications, and struggles post-cancer diagnosis, such as frustrations with physical weakness, lack of energy, and weight gain during chemotherapy. Participants displayed high levels of emotional and informational social support; creating a safe, empathetic environment for users to share positive and negative life experiences, sympathies, and motivation, as well as recommendations regarding various medications, oncologists, and YACS events. Users with shared or similar diagnoses seemed more inclined to share social support among each other; sometimes using humorous terms such as "lymphomies" and "cell mates". Soon after the trial began, participants began a thread sharing emails to add Fitbit friends list information amongst themselves for mutual encouragement and accountability to increase their exercise levels, and often discussed positive feelings of motivation from the group and seeing each other's activity levels in their Fitbit friends lists. In contrast, some threads described Fitbit lists and activities with non-cancer survivors as demotivating and mentioned withdrawing from them due to frustrations and damaging effects on self-esteem. This sense of othering from non-cancer survivors, a separation of identities before and after diagnosis, and need to establish new identities for themselves were discussed across several threads. Such comments were consistently met with empathy, encouragement, and personal anecdotes of struggles in display of solidarity. Over time, user conversation frequency on the Facebook page decreased, with new members enrolled via rolling recruitment forwarded to old threads of Fitbit friends list information and other conversation topics by more senior members, and most new posts relating to Fitbit issues and troubleshooting advice by the end of 6 months.
Discussion: This analysis represents a glimpse into the camaraderie and overall positive experiences YACS displayed in posts and comments within a private Facebook group in the context of a randomized trial of an mHealth intervention. Generally, participants shared motivation, high social support, and resources to promote physical activity and health without direction from study staff. Future planned analyses for this data involve expansion into the full 12-month duration of the self-help group, then content analysis and comparison to conversations in the

intervention group to determine if the types of conversations substantially differed between the two groups, and use all resulting interpretations to inform tailoring capabilities for future YACS mHealth interventions.

1:40-2:00 **Nathaniel Woodard, PhD, MPH**
Postdoc, Dr. Rachel Hirschey, Cancer Care Quality Training Program, Population Science
Title: The association between state-level structural racism and alcohol and tobacco use behaviors among a national probability sample of Black U.S. residents
Authors: Woodard N, Butler J, Ghosh D, Green KM, Knott CL
Abstract: Structural racism is how society maintains and promotes racial hierarchy and discrimination through established and interconnected systems. Structural racism is theorized to promote alcohol and tobacco use, that in turn contribute to observed health inequities, including those in cancer-health outcomes. The current study assesses the association between measures of state-level structural racism and alcohol and tobacco use among a national sample of 1,946 Black Americans. An existing composite index of state-level structural racism including five subscales (i.e., residential segregation and employment, economic, incarceration, and educational inequities) was merged with individual-level data from the national sample dataset. Hierarchical linear and logistic regression models, accounting for participant clustering at the state level, assessed the associations between structural racism and frequency of binge drinking and smoking frequency. Two models were estimated for each behavioral outcome, one using the composite structural racism index and one modeling measured dimensions of structural racism in lieu of the composite measure, each controlling for individual-level covariates. Results indicated a statistically significant positive association between the composite structural racism index and binge drinking behaviors and positive associations between the incarceration dimension and binge drinking frequency and smoking frequency. Results suggest that state-level structural racism, particularly that expressed in incarceration disparities, is positively associated with alcohol and tobacco use behaviors among Black Americans. Addressing structural racism, particularly in incarceration practices, through multilevel intervention and policy may help to reduce population-wide alcohol and tobacco use behaviors and improve the health outcomes of Black populations.

2:00-2:10pm
Break

2:10-3:00pm
Session 3 (A): Basic & Clinical/Translational Sciences
Hill Ballroom - Central & South, Zoom Session A
Chair: Kristina Drizyte-Miller, PhD

2:10-2:35 **Travis Nelson, PhD**
Postdoc, Chemical Biology and Medicinal Chemistry (CBMC), Nate Hathaway, UNC Integrated Translational Oncology Program, Clinical or Translational Research
Title: Targeted modulation of *TP53* expression with a small molecule epigenetic modifier & CRISPR/Cas9 to induce apoptosis
Authors: Nelson TJ, Kemper RM, Chiarella AM, Crona DJ, Hathaway NA
Abstract: Epigenetic dysregulation of gene expression is a common driver of a variety of human diseases, including cancer. Post-translational modifications of chromatin can result in abnormal regulation of key genes, leading to pathogenesis and a suppression of normal function. Of particular concern is the gene *TP53* and the tumor suppressing protein it encodes, p53. This transcription factor regulates signaling pathways that are associated with the maintenance of cellular homeostasis, response to cellular stresses, and tumor suppression. As such, *TP53* is mutated or epigenetically downregulated in many cancers and therefore makes for an attractive target for therapeutic upregulation. Current approaches towards epigenetic regulation largely rely small molecule drugs or large CRISPR/Cas9-based fusion proteins, which provide either a dose-dependent response or a gene-specific response, but not both. Recent work in our lab has focused on combining these two features to utilize the best of both worlds. We have engineered a system that combines a nuclease-deficient of CRISPR/Cas9 (dCas9), a guide RNA (gRNA), and a fusion protein containing the FK506 binding protein (FKBP), which links to a two-headed small molecule “chemical epigenetic modifier” (CEM). This final CEM component consists of FK506 linked to a

bromodomain inhibitor, and is thus designed to recruit a cell's endogenous epigenetic activators to a specific gene of interest. Here, we present preliminary work demonstrating that this dCas9-FKBP-CEM system to is capable of epigenetically upregulating *TP53* expression in a variety of cancer cell lines and is capable of inducing a significant shift towards apoptosis in a stomach cancer cell line.

2:35-3:00 **Susanna Stroik, PhD**
Postdoc, LCCC, Dale Ramsden, Integrated Training in Cancer Model Systems, Basic Science
Title: The Stepwise Actions of Polymerase Theta and Delta are Required for Alt-EJ
Authors: Susanna Stroik, Juan Carvajal - Garcia, Dipika Gupta, Alyssa Edwards, Adam Luthman, David W. Wyatt, Rachel L. Dannenberg, Wanjuan Feng, Thomas A. Kunkel, Gaorav P. Gupta, Mark Hedglin, Richard Wood, Sylvie Doublié, Eli Rothenberg, Dale A. Ramsden
Abstract: DNA double strand breaks (DSBs) are highly pathogenic DNA lesions which require resolution to maintain cellular viability. Homologous recombination (HR) and non-homologous end joining (NHEJ) are two well-defined pathways to repair DSBs and are responsible for the lion share of their repair. However, in the absence of either one of these two repair mechanisms, a third pathway, alternative end joining (Alt-EJ), becomes essential for viability and repair of DSBs. It is well established that the majority of Alt-EJ in mammals is dependent on Polymerase Theta. While it is appreciated that Pol Theta is required to identify and anneal microhomologies proximal to the DSB, it is unable to perform other key steps. Firstly, Alt-EJ requires a flap-trimming nuclease to eliminate the DNA flaps generated after annealing of microhomologies. Secondly, Theta is an error prone polymerase of dubious processivity which is unlikely capable of the breadth of synthesis required in Alt-EJ. We use a unique reporter system coupled with NGS to show here that while the initial ~30 nucleotides of synthesis is accomplished by Pol theta, a more processive and accurate polymerase must then take over. Using novel Alt-EJ reporter systems and separation of function mutations, we have identified Polymerase Delta's exonuclease function as essential for trimming flaps of various lengths in Alt-EJ, while its synthesis function is essential for continuation of DNA synthesis after the initial 30 nucleotides. We show these functions of Delta to be robust *in vitro*, in cells using extrachromosomal DNA substrates, and in the context of chromosomal Alt-EJ. The need to couple sequential steps in Alt-EJ together implies these two polymerases must form a physical unit, and we provide evidence for this complex using super resolution microscopy, biophysical assays, and Co-IP. In total, we show that Alt-EJ is mediated through the back-and-forth action of Polymerases Theta and Delta, with all four enzymatic activities of these two polymerases indispensable for pathway function.

2:10-3:00pm
Session 3 (B): Population Sciences
Hill Ballroom - North, Zoom Session B
Chair: Kenneth Busby III, DO

2:10-2:35 **Meghan O'Leary, PhD**
Postdoc, LCCC, Gita Mody, Cancer Care Quality Training Program, Population Science
Title: Assessing thoracic surgery patients' experiences with and motivations for completing postoperative ePRO monitoring to improve future implementation
Authors: O'Leary MC, Leeman J, Gentry A, Stover AM, Teal R, Vu MB, Carda-Auten J, Mody GN
Background: Electronic patient-reported outcome (ePRO) systems can be used to support postoperative patient care through digital symptom monitoring. We aimed to qualitatively assess patients' experiences with and motivations for completing ePROs following thoracic surgery. The goal is to use our qualitative findings to guide future implementation of ePRO symptom monitoring among thoracic surgery patients through a systems science approach.
Methods: Individual interviews with adult patients who previously underwent major thoracic surgery and monitored their postoperative symptoms via ePROs were conducted by phone and guided by the Capability, Opportunity, Motivation model for behavior change (COM-B). We wanted to understand their experiences completing 10-item symptom surveys up to twice weekly for 2 weeks and then weekly for 2 weeks after returning home, during which clinicians were alerted about concerning symptom burden. Interviews were audio recorded,

transcribed verbatim, and four team members used a coding-based content analysis to identify themes. We organized themes using COM-B through team discussion.
Results: Twenty-five patients were interviewed. Participants had a mean age of 58 years, were 56% female, 80% White, and 12% Black, and completed a mean of 5.2 out of 6 possible ePRO surveys. More than half (56%) had a history of lung cancer or another malignancy. With respect to capability, patients reported having the knowledge and skills to complete symptom surveys, though a subset described the physical and emotional energy required. In terms of opportunity, or the physical and social factors contributing to survey completion, participants explained that the ePRO interface and survey format, as well as being asked by their provider, facilitated their completion of the symptom surveys. Motivations included perceived individual benefits – specifically, accompaniment and a deepening connection with providers, care improvement (e.g., symptom management), and self-reflection (e.g., setting expectations, tracking progress) – and the opportunity to improve the larger system (e.g., by improving postoperative care and support for all patients). Factors that inhibited motivation included that the simplicity of the symptom surveys limited their fit to patients' individual experiences, and lack of clarity on how the symptom surveys would be used.
Discussion: Participants identified motivating factors for completing ePRO symptom surveys and described the experience of symptom monitoring as relatively feasible. We are now using process flow diagramming to design changes to implementation of ePRO symptom monitoring following thoracic surgery that address participant feedback. These changes include, for example, integrating process steps focused on patient education about the utility of symptom surveys and establishing expectations for symptom burden during the pre-operative period. Future work should consider how to capture patients' complex health experiences in the symptom surveys.

2:35-3:00 **Eman Metwally, MD-PhD, MSCR**
Postdoc, Epidemiology-Gilling, Caroline Thompson, Population and Translational Science
Title: Emergency Diagnosis of Lung Cancer Among Patients with Chronic Obstructive Pulmonary Disease in The United States
Authors: Metwally EM[1,2], M. Bradley Drummond[3], Sharon Peacock Hinton[1], Caroline A. Thompson. [1,2,4]
Authors Affiliations:
[1] Department of Epidemiology, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
[2] Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
[3] Division of Pulmonary Diseases and Critical Care Medicine, School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
[4] Center for Health Promotion and Disease Prevention, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
Background: Diagnosis of lung cancer during acute inpatient hospitalization after emergency department visit (heretofore "Emergency diagnosis of lung cancer" (EDLC)) has been associated with late-stage diagnosis and poorer survival, especially among patients with multimorbidity and disadvantaged racial and socioeconomic backgrounds. COPD is a common comorbidity among patients with lung cancer and is itself a frequent cause of emergency department visits.
Objectives: We sought to characterize prevalence, sociodemographic, clinical, and surgical treatment of emergency vs. non-emergency diagnosed lung cancer among patients with comorbid COPD. We quantified the association between emergency diagnosis of lung cancer and COPD, overall and by race and socioeconomic status (SES). Further, we quantified this association among patients with COPD with versus without acute exacerbation (AECOPD).
Methods: We conducted a secondary data analysis using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) linked to Medicare database including Medicare beneficiaries aged 66+ years with primary invasive lung cancer diagnosed from 2008 to 2017 who were alive at the time of lung cancer diagnosis and had

continuous Medicare coverage from 12 months prior to 3 months after lung cancer diagnosis, or until death. **Exposure:** Comorbid COPD diagnosis was determined using ICD-9, ICD-10 diagnosis codes in Medicare claims during the 12 months prior to 3 months after lung cancer diagnosis. **Outcome:** Emergency diagnosis was defined as diagnosis of lung cancer during acute inpatient hospitalization following emergency department visit. **Statistical analysis:** We used generalized linear models to estimate adjusted absolute (prevalence difference) and relative (prevalence ratio) association with emergency diagnosis of lung cancer.
Results: Among 185,405 Medicare beneficiaries with lung cancer, 131,230 (70.8%) had COPD, of them 33,707 (25.7%) had emergency diagnosis of their lung cancer. Among patients with comorbid COPD, those with versus without emergency diagnosis of lung cancer were more likely to be non-Hispanic Black, Hispanic, and had lower census-tract SES. Clinically, they had more comorbidities especially diabetes, and congestive heart failure, were frailer, had more small cell lung cancer, more late-stage cancer, and less primary surgical treatment of lung cancer. We observed a positive association between COPD and emergency diagnosis of lung cancer that persisted after adjusting for age, sex, year of lung cancer diagnosis, and SEER registry region (prevalence ratio= 1.28, 95% CI= 1.25 to 1.31). Among patients with comorbid COPD, there was a positive association between AECOPD and emergency diagnosis of lung cancer (prevalence ratio= 1.76, 95% CI= 1.71 to 1.80). These associations were stronger for patients with non-Hispanic White (vs. NHB and Hispanic) race/ ethnicity, and for patients with highest (vs. Lowest) SES.
Conclusion: Approximately one out of four lung cancer diagnoses occur during acute inpatient hospitalization following emergency department visit among elderly patients in the US. Patients with versus without COPD are at higher risk of emergency diagnosis of lung cancer and its poor cancer outcomes (late-stage diagnosis and less surgical treatment). Beyond established risk factors for EDLC, AECOPD is a novel and important risk factor we identified which should be incorporated into screening protocols of lung cancer detection.

3:00-3:15pm
Patty Spears, BS, FASCO
Patient Advocate, Translational Science and Health Services, Community Outreach and Engagement
Title: Engaging Patient and Community Advocates in Cancer Research
Hill Ballroom Central & South, Zoom Session A

3:15-4:00pm
Poster Session (A)
Chancellor's Ballroom

Poster# A001
Tara Walhart, PhD, NP-C
Postdoc, Microbiology and Immunology, Dotti Lab/Gianpietro Dotti, Cancer Epigenetics Training Grant, Clinical or Translational Research
Title: Cathepsin G directed CAR T-cells Targeting Acute Myeloid Leukemia
Authors: Walhart T, Biondi M, Stucchi S, Li G, Song F, Shou P, Withers T, Armistead P, Su L, Solvaldo B, Dotti G
Abstract: Patients with relapsed and refractory acute myeloid leukemia (AML) have limited therapeutic options. Following the clinical success of CD19-directed chimeric antigen receptor (CAR) T-cell treatment in acute lymphoblastic leukemia, efforts have been made to duplicate these results in AML. However, the development of CAR-T cells targeting AML is challenging because AML lacks antigens exclusively expressed on the cell surface of leukemic blasts, with the consequence of potential life-threatening myelosuppression. In contrast, intracytoplasmic myeloid-associated antigens such as WT1 that are overexpressed by AML blasts are usually targeted by T cells genetically modified to express conventional T-Cell Receptor (TCR)/MHC restricted. Here we asked the question if intracytoplasmic myeloid antigens MHC restricted can be targeted by CAR-T cells. Specifically, we have identified an abundant HLA-A2-restricted peptide derived from Cathepsin-G (CG1) in AML and developed a

scFv that specifically recognizes the peptide in the contest of HLA-A2. Our preliminary data indicate the CG1.CAR-T cells show anti-tumor-killing ability *in vitro*. However, the functional avidity of the CG1.CAR is inferior to the avidity of conventional aßTCR receptors targeting MHC Class I restricted peptides. Therefore, we sought to enhance the functional avidity of the CG1.CAR by 1) enhancing the proximal signal strength by including an additional immunoreceptor tyrosine-based activation motif (ITAM) and 2) overexpression of the LCK-kinase molecule to promote enhanced phosphorylation of the ITAM. Our results indicate the enhanced CG10.CAR displays increased avidity and anti-tumor-killing ability and prolongs the overall survival of tumor-bearing mice without causing toxicity to the hematopoietic compartment. These studies will be instrumental to enable the development of the Investigational New Drug (IND) and clinical translation.

Poster# A002

Priya Hibshman, PhD Candidate

Graduate Student, Cell Biology & Physiology, Dr. Channing J. Der, Basic Science

Title: Defining the role of MYC in KRAS-dependent pancreatic cancer.

Authors: Priya S. Hibshman[1], Clint A. Stalnecker[2], Kristina Drizyte-Miller[3], J. Nathaniel Diehl[4], Richard G. Hodge[3], Craig M. Goodwin[3], Jeff A. Klomp[2], Sen Peng[5], Natalie K. Barker[6], Mariaelena Pierobon[7], Nhan L. Tran[8], Laura A. Herring[6], Lee M. Graves[2], Emanuel F. Petricoin III[7], Kirsten L. Bryant[2,3], Adrienne D. Cox[1,2,3,9], and Channing J. Der[1,2,3,4]

[1]Cell Biology and Physiology Curriculum, [2]Department of Pharmacology [3]Lineberger Comprehensive Cancer Center, [4]Curriculum in Genetics and Molecular Biology, [6]Michael Hooker Proteomics Center, and Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Illumina, Inc., San Diego, CA; [7]Center for Applied Proteomics and Molecular Medicine, George Mason University, Fairfax, VA; [8]Department of Cancer Biology, Mayo Clinic Arizona, Scottsdale, AZ

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the United States and standards-of-care are limited to ineffective cytotoxic chemotherapy. Mutationally activated KRAS is found in 95% of cases and drives PDAC growth predominantly through activation of the ERK mitogen-activated protein kinase (MAPK) cascade. Despite the key role of this signaling pathway, how ERK MAPK signaling supports KRAS-dependent PDAC growth remains to be established. While ERK regulates a complex phosphoproteome (>2000 direct/indirect substrates), we hypothesized that one substrate, the MYC oncoprotein and transcription factor, is the critical driver of KRAS- and ERK-dependent PDAC growth. We first applied reverse phase protein array (RPPA) analyses and determined that KRAS and MYC regulate significantly overlapping oncogenic signaling networks. Then, to delineate the contribution of MYC to KRAS-driven PDAC and establish a system-wide profile of the MYC-dependent transcriptome, we applied RNA-sequencing of PDAC cells with acute siRNA suppression of MYC. Gene set enrichment analysis determined that MYC-regulated genes control diverse KRAS-driven cellular processes. We then used genetic suppression of KRAS or MYC to validate these processes, including RHO small GTPase activation, EMT, mitochondrial dynamics, and autophagy. Our ongoing analyses have profiled the KRAS- and MYC-regulated kinome to assess the involvement of MYC in KRAS-driven kinome remodeling in PDAC. In summary, our studies establish a significant role for MYC in diverse KRAS-driven cellular activities and support the provocative concept that inhibiting MYC function may be an effective strategy for targeting KRAS for PDAC treatment.

Poster# A003

Margarita Dzama, PhD

Postdoc, Genetics, Jesse Raab, Basic Science

Title: *Identification of epigenetic therapies for liver cancer*

Authors: Dzama MM, Kuhlers P, Raab JR

Abstract: Liver cancer is the third leading cause of cancer-related death worldwide with hepatocellular carcinoma (HCC) being the most common primary liver cancer (~90%). The majority of patients are diagnosed at advanced stages of HCC, with the 5-year survival rate being about 18%. Late prognosis leaves patient with a few available systemic therapy options, which show only marginal to moderate clinical benefit. The lack of more efficient therapies is one of the major contributors to the high mortality rate of HCC. Whole-exome and whole-genome sequencing of liver cancer samples has revealed mutations in epigenetic modifiers in about 50% of HCC. A number of chromatin regulators have been also shown to play an important role in sensitizing the therapy response against various cancers.

Therefore, in this project, we are focused on identifying new therapeutic targets of HCC among epigenetic modifiers and evaluating them as potential targets for future drug development.
We constructed a CRISPR library of 6000 guide RNAs (gRNAs) targeting 737 genes involved in chromatin-mediated gene regulation. Using this epigenome-focused CRISPR/Cas9 screening in two-dimensional (2D) and three-dimensional (3D) settings in several liver cancer cell lines (HepG2, HLF, PLC/PRF/5), we identified a list of epigenetic regulators as potential new targets in HCC. We focused our research on two of them, *MEN1* and *ASH2L*, which are core subunits of the menin-MLL complex mediating H3K4 trimethylation, a histone post-translation modification known to be associated with active transcription. We validated potential dependencies of HCC on *MEN1* and *ASH2L* using a competitive growth assay in HLF and PLC/PRF/5 cell lines. Next, we pharmacologically inhibited the menin-MLL interaction in several HCC cell lines (HLF, PLC/PRF/5, HepG2) and a normal liver cell line (AML12) by using recently developed menin inhibitor SNDX-5613 (revumenib). While we observed a dose-dependent reduction in cell proliferation upon menin inhibition in all HCC cell lines, AML12 cells showed an increase in cell proliferation.
In order to explore transcriptional changes associated with disruption of menin-MLL complex, we performed RNA sequencing (RNA-seq) of HLF cells following either inhibition with SNDX-5613 for 4 days or knock out of *MEN1* gene. We identified that both knockout (KO) of *MEN1* gene and its protein inhibition upregulate KRAS signaling and oncogenic signature of TGF-beta signaling. To determine potential synergistic combinatorial treatments when combined with menin inhibition, we performed a 3D epigenome-focused CRISPR/Cas9 screening in the presence of SNDX-5613 drug. A member of Polycomb group proteins, CBX4, was one of the identified targets sensitizing the treatment to SNDX-5613. This result suggests a potential interaction between Polycomb and menin-MLL complexes, which might be important for HCC cell survival. We are currently testing the synergy between inhibition of menin
Altogether, we anticipate that menin and ASH2L might serve as promising targets and represent an appealing therapeutic strategy for HCC treatment. We believe that a better understanding of the oncogenic mechanisms of menin and ASH2L in HCC may help in the development of rational treatment strategies and improve the treatment outcome.

Poster# A004
Amy Pomeroy, PhD
Postdoc, Pharmacology, Computational Medicine, Adam Palmer, Clinical or Translational Research
Title: A model of combination therapy explains and predicts lymphoma clinical trial results
Authors: Amy E. Pomeroy[1] and Adam C. Palmer[1]
[1] Department of Pharmacology, Computational Medicine Program, UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
Abstract: Combinations of chemotherapies elicit higher cure rates and longer responses than single drugs. Several rationales contribute to combinations' efficacy, including overcoming patient and tumor heterogeneity and improving efficacy through favorable pharmacological effects. We present a quantitative model that unifies these phenomena to simulate and understand the clinical activity of drug combinations by describing kinetics of tumor growth and death in response to treatment and outputting Progression-Free Survival (PFS) distributions. We applied this model to combination therapy for Diffuse Large B-Cell Lymphoma (DLBCL), which is cured in most patients by the 5-drug combination RCHOP. Our simulation reproduces multiple clinical outcomes including PFS distributions and tumor shrinkage kinetics in patients. We tested the prospective utility of this model by predicting the result of a clinical trial. Specifically, we used a clinical trial of Polatuzumab-Vedotin (PV) in relapsed/refractory (r/r) DLBCL to calibrate model parameters for the activity of PV and simulated a clinical trial adding PV to the RCHOP combination. The phase 3 trial results for this combination later showed that our model accurately predicted the improvement in PFS. Additionally, we retrospectively analyzed six trials that aimed to improve first-line DLBCL treatment and determined that, based on the single drug efficacies in r/r DLBCL, these trials' results were predictable by the simulation. These results show that curative combinatory treatments can be understood in quantitative and kinetic detail, and simulations can be applied prospectively to predict the clinical efficacy of novel combinations informing trial design to prioritize new regimens.

Poster# A005
Claire (I-Hsuan) Su, MS
Graduate Student, Epidemiology, Dr. Jennifer Lund, Population Science - Public Health
Title: Evaluating uptake of lung cancer screening in the United States (US) from 2017-2021

Background: Lung cancer screening by low-dose computed tomography (LDCT) reduces lung cancer mortality through earlier diagnosis and treatment. While the US Preventative Services Task Force (USPSTF) issued a grade B recommendation for annual LDCT to those who are at high risk based on age and smoking history, uptake in clinical practice is low.
Objectives To describe contemporary patterns of lung cancer screening uptake in the US from 2017 to 2021.
Methods: We used data from the Centers for Disease Control and Prevention's 2017-2021 Behavioral Risk Factor Surveillance System (BRFSS). Screening eligibility was determined per USPSTF 2013 recommendation of those ages 55-80 years who are current or former (quit within the last 15 years) smokers with a smoking history of ≥30 pack-years. Current age of respondent, smoking status, and sociodemographic and clinical characteristics were obtained from the BRFSS standard core component questions. Age at smoking initiation, age when last smoked regularly, average number of cigarettes smoked per day, and whether respondent had a CT scan in the past year to check for lung cancer were ascertained from the BRFSS optional lung cancer screening module. The number of years smoked was obtained by subtracting the age of smoking initiation from the age last smoked regularly for former smokers and from current age for current smokers. Pack-years of smoking were calculated by dividing the average number of cigarettes smoked per day by 20 and multiplying by the number of years smoked. Weighted frequencies and means were calculated to assess LDCT screening utilization across calendar year and by sociodemographic characteristics, accounting for survey sampling.
Results: There were 11, 8, 20, 5, and 7 states that participated in the BFRSS- Lung Cancer Screening module from 2017-2021. Over the study period, 3-4% of individuals were eligible for lung cancer screening. The weighted percentage of screened individuals among those eligible were 14%, 18%, 15%, 19%, 19%, respectively. The median age among those screened ranged from 62 in 2018 to 66 in 2021. Among those under age 65 eligible for screening, the weighted percentage of individuals screened was the lowest (11%) in 2017, rose to 18% in 2018, and hovered around 13-15% in 2019-2021. Among the non-Hispanic Black population eligible for screening, the weighted percentage of individuals screened remained under 16% from 2017 to 2019 but rose to 20% in 2020. Among the uninsured eligible population, screening uptake was low, varying around 5% in all years.
Conclusions: Lung cancer screening uptake continues to remain low. Targeted screening outreach is needed for specific subgroups, defined by race and ethnicity and insurance status, to increase equitable access to early cancer treatment that can improve outcomes.

Poster# A006
Merrill Froney
Graduate Student, School of Pharmacy, Samantha G. Pattenden, Basic Science
Title: Development of a platform for therapeutic target discovery for alternative lengthening of telomeres (ALT) cancers
Authors: Merrill Froney, Christian Cook, Alyssa Cadiz, Brian Golitz, Katherine Flinter, Bianca Chan, Brian Hardy, Ally Wardell, Michael Jarstfer, Samantha Pattenden
Abstract: Telomeric DNA acts as a protective cap to prevent chromosome ends from being recognized as double stranded breaks during DNA replication. In somatic cells, telomeres are shortened with each cell division due to telomere erosion, which eventually leads to senescence. This process is a checkpoint to prevent uncontrolled cell growth. Tumor cells avoid telomere shortening by activating one of two telomere maintenance mechanisms (TMMs): telomerase reactivation or alternative lengthening of telomeres (ALT). TMMs are a viable target for cancer treatment, as they are not active in normal cells. While there is a telomerase inhibitor currently undergoing clinical trials, there are no known ALT inhibitors in development, partially because ALT is a complex and poorly understood pathway. For neuroblastoma and osteosarcoma, an ALT-positive status is associated with an aggressive phenotype that has few therapeutic options. Thus, there is a biological and clinical need to develop ALT specific chemical probes that will give insight into ALT biology and assess ALT-specific therapeutic targets. To fulfil these unmet needs, we have developed a first-in-class ALT specific phenotypic high throughput screen to identify inhibitors of ALT activity. Our screen measures relative C-circle level, an ALT-specific biomarker, to detect ALT inhibition induced by compound treatment. We screened osteosarcoma and neuroblastoma ALT-positive cell lines against epigenetically targeted compound libraries to investigate the role chromatin dynamics plays in the pathway. Overall, this approach will increase understanding of ALT biology and expand the repertoire of potential ALT-specific therapeutic targets.

Poster# A007

Mohamed Attia, PhD

Postdoc, DPMP Eshelman School of Pharmacy, Alexander Kabanov, Clinical or Translational Research

Title:

Abstract:

Poster# A008

Deniz Coskuner, MD

Postdoc, CGIBD, School of Medicine, Aadra Bhatt, Basic Science

Title: Using *in vitro* tools to assess gastrointestinal toxicity of drugs reactivated by gut bacteria

Background: Gastrointestinal toxicity (GIT) including vomiting and diarrhea are among the most common side-effects of investigational and FDA-approved oncotherapeutics. Minor side effects are treated symptomatically, but severe GIT requires either dose reduction or change of oncotherapeutic, thus impacting treatment efficacy. There are limited tools to predict GIT, each with inherent limitations. The utility of primary human epithelial cell culture (1^{O} hIEC) platforms mimicking the two-compartment structure of intestinal lumen is rapidly increasing.

Intestinal bacteria directly modify >300 orally ingested drugs and can also reactivate Phase II conjugates arising from host drug metabolism through bacterial β- glucuronidase (GUS) enzymes. GUS hydrolysis of drug-glucuronide conjugates results in reactivated compounds that can be locally or systemically toxic. We have developed a static point-estimation of luminal concentrations of oral chemotherapeutics known to be glucuronidated, to test relevant doses of drugs reactivated by the gut microbiota.

Aim: Our aim is to use this model to test GIT in 1^{O} hIEC that occurs due to drug reactivation via GUS enzymes.

Hypothesis: Reactivated drug conjugates exert epithelial damage.

Methods: We exposed 1° proliferating or differentiated hIECs (ileal) to FDA-approved drugs and measured various readouts of cellular health.

Results: The model showed epithelial distress in 14/16 drugs with reported GIT.

Conclusion: Bacterial GUS reactivation of drug-glucuronide conjugates can damage barrier integrity, increase permeability, and cause cytotoxicity. Drug metabolism by gut microbiota should be an important consideration during drug development, and it can be predicted *in vitro* via 1°hIEC cultures.

Poster# A009

Alexander Cole Edwards

Graduate Student, Cell Biology and Physiology, Dr. Channing J. Der, UNC MiBio T32, Clinical or Translational Research

Title: TEAD inhibition overcomes YAP1/TAZ-driven intrinsic and acquired resistance to $KRAS^{G12C}$ inhibitors

Authors: A. Cole Edwards[1], Clint A. Stalnecker[4], Alexis J. Morales[3,4], Khalilah E. Taylor[4], Jill Hallin[5], Tracy T. Tang[7], Lars D. Engstrom[5], Adam Pavlicek[6], Leonard Post[7], Peter Olson[5], James G. Christensen[5], Adrienne D. Cox[1,2,3,4] and Channing J. Der[1,3,4]

Abstract: Departments of [1]Cell Biology and Physiology, [2]Radiation Oncology and [3]Pharmacology, [4]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Mirati Therapeutics, Inc., San Diego, CA, [6]Monoceros Biosystems LLC, San Diego, CA, [7]Vivace Therapeutics, Inc., San Mateo, CA

Activated mutants of *KRAS* comprise the major oncogenic drivers in lung (LAC), colorectal (CRC), and pancreatic ductal (PDAC) adenocarcinoma. Recent success in covalently targeting one KRAS mutant ($KRAS^{G12C}$) led to FDA approval of the first anti-KRAS therapy (G12Ci). However, both primary and treatment-induced acquired resistance to G12Ci have been observed. While analyses of relapsed patients have identified reactivation of the key KRAS effector signaling network as a driver of resistance, the mechanisms in ~50% of patients are not known. To identify potential resistance mechanisms, we applied a CRISPR-Cas9 loss-of-function screen targeting the druggable genome. In addition to genes discovered recently in relapsed patients (e.g., *PTEN*, *NF1*), we also identified loss of multiple components of the Hippo tumor suppressor pathway as drivers of G12Ci resistance (*NF2, LATS1/2, TAOK1/*2 and *STK3/4*). We therefore determined if activation of the functionally related transcriptional co-activators, YAP1 and TAZ, normally inhibited by Hippo signaling, can drive resistance to G12Ci. We first determined that ectopic expression of constitutively activated YAP1/TAZ was sufficient to impair the anti-proliferative and pro-apoptotic effects of G12Ci

treatment in $KRAS^{G12C}$-mutant LAC, CRC, and PDAC cell lines. Conversely, genetic suppression of *YAP1/TAZ* enhanced G12Ci sensitivity. YAP1/TAZ requires association with TEAD and other transcription factors to regulate transcription. We determined that YAP1/TAZ mutants deficient in TEAD binding failed to drive resistance to G12Ci treatment. Further supporting a role for TEAD, both overexpression of a TEAD dominant negative mutant and treatment with pan-TEAD pharmacological inhibitors phenocopied the effects of *YAP1/TAZ* genetic suppression and sensitized $KRAS^{G12C}$ mutant cancer cells to G12Ci. Finally, transcriptional analyses support a model where YAP1/TAZ-TEAD overcomes $KRAS^{G12C}$ addiction by restoring a subset of KRAS-dependent gene transcription. In summary, our observations support YAP1/TAZ-TEAD signaling as a novel driver of resistance to KRAS inhibition and support the use of TEAD inhibitors to enhance the anti-tumor efficacy of KRAS-targeted therapies.

Poster# A010

Matthew Dunn, MPH

Graduate Student, Epidemiology, Cancer Care Quality Training Program, Population Science (Public Health)

Title: Understanding mechanisms of racial disparities in breast cancer: an assessment of screening and regular care in the Carolina Breast Cancer Study

Authors: Matthew R Dunn, Eman M Metwally, Sanah Vohra, Terry Hyslop, Louise M Henderson, Katie Reeder-Hayes, Caroline A Thompson, Jennifer Elston Lafata, Melissa A Troester, Eboneé N Butler

Background: Early detection of breast cancer is associated with less advanced disease at diagnosis and improved prognosis. Given persistent racial disparities in breast cancer survivorship, understanding how screening and reliable access to care can support earlier detection – especially among Black women – is a public health priority.

Objective: We aimed to identify how screening history and regular healthcare were correlated to tumor characteristics at diagnosis in a screening-eligible (45-74 years old) population of Black and non-Black women in North Carolina.

Methods: The analysis included 2,058 women aged 45 years and older (49% Black) from the Carolina Breast Cancer Study phase 3 (CBCS3), a population-based cohort of women diagnosed with invasive breast cancer between 2008-2013. Screening history and usual patterns of health care utilization (henceforth "regular care") were assessed by self-report and classified as binary exposures: screening-adherent (defined as greater or less than 0.5 mammograms per year) and regular care (i.e., reported reliance on healthcare in office-based settings rather than urgent or emergency care), respectively. The relationship between each exposure and tumor stage, size, and grade at diagnosis, as well as mode of detection (noticed lump vs routine mammogram), were assessed by log-binomial regression and expressed as relative risks (RRs) and risk differences (RDs) with 95% confidence intervals. Results were presented overall and stratified by race.

Results: Participants lacking both screening and regular care (compared to those with both) were more likely to be diagnosed with unfavorable tumor characteristics: tumor size 5+ cm (RR, CI = 2.51, 1.76- 3.56), advanced stage (RR , CI= 3.15, 2.15-4.63), and lump detection (RR, CI =1.84, 1.63-2.06); the magnitude of these associations were highest for Black women. However, among screening adherent participants, racial differences in stage, size, and mode of detection were attenuated. Notably, the prevalence of large tumor size (>5 cm) comparing Black and non-Black participants in the screening non-adherent strata (19.6% and 11.5%, RD=8.1%) was reduced when we restricted the analysis to screening-adherent participants (10.0% vs 7.2%, RD=2.8%). Similarly, racial differences in advanced stage (Stage 3B+) presentation were also reduced from (16.3% vs 10.8%, RD=5.5%) to (6.5% vs 5.1%, RD=1.4%).

Conclusions: Non-adherence to biennial screening and the absence of regular care were associated with unfavorable tumor characteristics at diagnosis among both Black and non-Black women. Black women had higher absolute risks for large tumors at diagnosis, advanced stage at diagnosis, and lump-detected breast cancers across both categories of care; however, screening adherence attenuated risk differences by race. Improving screening adherence and access to regular care may be points of intervention to advance health equity among breast cancer survivors.

Informational Poster

Patty Spears, BS, FASCO

Patient Advocate, Translational Science and Health Services, Community Outreach and Engagement

Title: Researcher and Advocate Partnerships at Lineberger Comprehensive Cancer Center

Description: The Lineberger Excellence in Advocacy Program (LEAP) brings patient and community advocate experiences to researchers at Lineberger Comprehensive Cancer Center.

Poster# A011

William David Green, PhD

Postdoc, Microbiology & Immunology, Justin Milner, Carolina Cancer Nanotechnology Training Program, Basic Science

Title: Exhausted CD8 T cells adapt to distinct tumor microenvironments through shared and discrete molecular programs

Authors: Green, WD., Plotkin, A., Gomez, A., Pratt, B., Zhabotynsky, V., Mullins, GN., Green, JM., Cannon, G., Stanley, N., Hursting, S., Pylayeva-Gupta, Y., Baldwin, AS., and Milner JJ.

Abstract: CD8 T lymphocytes control infection and malignancy through differentiation into specialized cell states with discrete functional attributes. While CD8 T cell fate commitment is a transcriptionally and epigenetically controlled process, the transcription factors and chromatin modifiers governing CD8 T cell differentiation remain ill-defined. Here, we leveraged mouse models of viral infection and cancer to simultaneous profile the chromatin and transcriptomic landscapes of virus-specific and tumor-specific CD8 T cells at single-cell resolution. Through in-depth comparison of antigen-specific CD8 T cells across distinct disease settings, we define uncharacterized CD8 T cell states and clarify roles for molecular regulators of T cell heterogeneity. Comparison of uniquely accessible regions of chromatin along with predicted transcription factor activity uncover regulatory networks that both guide and enforce CD8 T cell fate commitment into novel and established states spanning T cell memory, residency, and exhaustion. Further, we have functionally defined novel roles for several transcriptional regulators in controlling CD8 T differentiation during infection and cancer, including undescribed roles for the transcription factor *Klf2*. Together, our findings clarify CD8 T cell heterogeneity and differentiation trajectories across acute infection, chronic infection, and cancer. We show our findings can be leveraged to enhance promising immunotherapy approaches.

Poster# A012

Mallory Roach

Graduate Student, Pharmacology, Dr. Kirsten Bryant, Clinical or Translational Research

Title: Vertical inhibition of autophagy as a therapeutic strategy for pancreatic ductal adenocarcinoma

Authors: Mallory K. Roach[1], Jonathan M. DeLiberty[1], Noah L. Pieper[2], Kirsten L. Bryant[1,2]

[1]Department of Pharmacology, [2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is third leading cause of cancer death in the United States. Mutational activation by KRAS if often the initiating genetic event of these tumors with greater than 90% of PDAC harboring mutations in this oncogene. Our group and others demonstrated that inhibition of the RAF/MEK/ERK pathway in PDAC induces an increased dependence on autophagy, a metabolic nutrient scavenging process by which cellular components are recycled in times of nutrient stress. Combined inhibition of the ERK MAPK pathway and autophagy inhibited the growth of multiple preclinical models of PDAC. Based on these findings, combined ERK/MEK inhibition and hydroxychloroquine (HCQ) is currently under clinical evaluation (NCT03825289, NCT04386057).

However, evidence of resistance to this therapeutic combination has been reported. Our lab recently performed a CRISPR-Cas9 mediated loss-of-function screen to identify sensitizers to CQ treatment. Surprisingly, we identified multiple autophagy related genes, indicating that dual inhibition of multiple nodes of the autophagy pathway via CQ and other druggable components upstream may be a more effective method of inhibiting autophagy in PDAC. PIK3C3, the gene that encodes for VPS34, a protein essential for the nucleation phase of the autophagic pathway, was identified as a potential sensitizer to CQ treatment. These results prompted us to hypothesize that ULK1, a serine/threonine kinase critical for the induction of autophagy, is a potential upstream target. We found that both ULK inhibition and VPS34 inhibition sensitized PDAC cells to CQ treatment and treatment with apilimod, a chemically distinct end of the autophagic pathway inhibitor. Finally, vertical inhibition of the autophagic pathway via ULK1 inhibition and CQ displayed synergy with ERK inhibition to further reduce PDAC proliferation. Ongoing and future studies are aimed at extending this observation to include direct RAS inhibition, as well as mechanistically understanding the effect of vertical autophagy inhibition on reducing autophagic flux.

Poster# A013

Rina Yarosh, MPH

Graduate Student, Epidemiology, Hazel Nichols, Eboneé Butler*, Population Science - Public Health*

Title: Late effects of breast cancer treatment among long term breast cancer survivors in the Carolina Breast Cancer Study

Authors: Rina A. Yarosh[1], Hazel B. Nichols[1,2], Rachel Hirschey[2,3], Erin E. Kent[2,4], Lisa A. Carey[2], Melissa A. Troester[1,2], Eboneé N. Butler[1,2]

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Background: Improved precision in breast cancer treatment has contributed to better overall survival. Intensive breast cancer treatments may have long-term impacts on survivor quality of life. Survivors may experience late effects including lymphedema, peripheral neuropathy, and cardiotoxicity from surgery, radiation, or chemotherapy. Estimates of the long-term burden of chronic breast cancer related conditions are important for managing the care of survivors.

Methods: The Carolina Breast Cancer Study 3 is a population-based study of female breast cancer survivors diagnosed from 2008 to 2013 in North Carolina. Black and younger (<50 years at diagnosis) women were oversampled. We calculated the cumulative prevalence of self-reporting of ever being diagnosed with lymphedema, peripheral neuropathy, or cardiac/ heart problems as a result of breast cancer treatment over a 10-year follow-up period. Prevalence differences (PD) and 95% confidence intervals (CI), adjusted for age and race, were calculated to describe the differences in late effects in relation to patient characteristics (including latent class SES and access to care barriers). Additionally, we assessed racial disparities in the prevalence of late effects.

Results: We included 1133 women who completed follow-up assessments at a mean of 11.2 years (SD=0.5) post diagnosis. The sample was predominately diagnosed with early stage (89.2%) and ER+ disease (75.2%). Treatments included lymph node removal (>5 lymph nodes 57.9%), anthracycline chemotherapy (34.1%), taxane chemotherapy (60.3%), breast conserving surgery (58.7%), and mastectomy (41.0%). The prevalence of self-reporting lymphedema was 39.9% and was more common among younger (<50 vs ≥50 PD: 10.2%, CI 4.7-15.7) and Black women (vs. White PD: 19.1%, CI 13.5-24.7), and those with fewer access to care barriers (vs more PD: -19.5%, CI -31.1- -8). The prevalence of peripheral neuropathy was 64.9% and was more common among younger (<50 vs ≥50 PD: 5.6%, CI 0.2-11.0) and Black women (vs. White PD: 16.5%, CI 11.1-21.9), and those of lower SES (high vs low PD: -11.7%, CI -17.6- -5.7). Rural survivors were less likely to report peripheral neuropathy (PD: -9.7%, CI: -17.5- -2.0). Cardiac problems were reported in 16.7% of the sample and were more common among those of high SES (vs. low PD: -7.7%, CI -12.5, -3.0).

All three late effects were associated with higher stage disease, ER+ disease, number of lymph nodes removed, anthracycline chemotherapy, and taxane chemotherapy. Both lymphedema and peripheral neuropathy were associated with mastectomy. Lymphedema was associated with trastuzumab use. Peripheral neuropathy was associated with recurrence.

In stratified analyses by ER status, Black women were 13.7-28.8% more likely to have lymphedema in both ER+ and ER- disease (ER+ PD Black vs. White: 13.7%, CI 7.9-20.3; ER- PD Black vs. White: 28.8%, CI 18.3-39.3). Similar patterns were seen in analyses stratified by number of lymph nodes removed and by taxane chemotherapy. Other associations were not suggestive of racial disparities; with one exception. Black women were more likely to have cardiac problems at both high and low levels of SES (High Black vs White PD: 2.8%, CI -3.0, 8.6; low Black vs White PD: -7.0%, CI -15.2, 1.2).

Conclusions: This study identified patient characteristics associated with an increased burden of late effects. Black and younger women experience a higher burden of lymphedema and peripheral neuropathy. Disease stage, ER status, lymph nodes removed, and chemotherapy received were associated with a higher prevalence of all three late effects and this is consistent with the observation that the burden of late effects increases with factors associated with more advanced stage of disease. Improved surveillance and prevention measures for breast cancer late effects can help improve survivorship care.

Poster# A014

Sirui Li, PhD

Postdoc, LCCC, Jenny Ting, Basic Science

Title: STING-induced B regulatory cells compromise NK function in cancer immunity

Authors: Sirui Li[1,2,3*], Bhalchandra Mirlekar[1,2*], Brandon M. Johnson[1,3] , W. June Brickey[1,3], John A. Wrobel[1,2,3], Na Yang[4], Dingka Song[3,+], Sarah Entwistle[1,5], Xianming Tan[1], Meng Deng[1,6], Ya Cui[7], Wei Li[7], Benjamin G. Vincent[1,5], Michael Gale, Jr.[8], Yuliya Pylayeva-Gupta[1,2#], Jenny P.-Y. Ting[1,2,3,6#]

Abstract: An immunosuppressive tumor microenvironment is a major obstacle in the control of pancreatic and other solid cancers. STING (stimulator of interferon genes) agonists trigger inflammatory innate immune responses to potentially overcome tumor immunosuppression. Although these agonists hold promise as potential cancer therapies, tumor resistance to STING monotherapy has emerged in clinical trials and the mechanism(s) are unclear. We show that the administration of five distinct STING agonists, including cGAMP, results in an expansion of human and mouse IL-35+ regulatory B lymphocytes in pancreatic cancer. Mechanistically, cGAMP drives B cell IL-35 expression in an IRF3-dependent but type I interferon-independent manner. In multiple preclinical cancer models, the loss of STING signaling in B cells increases tumor control. Furthermore, IL-35 blockade or genetic ablation of IL-35 in B cells also reduces tumor growth. Unexpectedly, the STING-IL-35 axis in B cells reduces NK proliferation and attenuates NK-driven anti-tumor response. These findings reveal an intrinsic barrier to systemic STING agonist monotherapy and provide a novel combinatorial strategy to overcome immunosuppression in tumors.

Poster# A015

Kristina Drizyte-Miller, PhD

Postdoc, LCCC, Channing Der, Basic Science

Title: Identification and validation of novel combinations for direct RAS inhibitors for the treatment of KRAS-mutant pancreatic cancer

Authors: Kristina Drizyte-Miller[1], Wen-Hsuan Chang[1], Andrew M. Waters[2], Amber A. Amparo[1], Ye Lee[3], Priya S. Hibshman[4], Clint A. Stalnecker[1,3], Adrienne D. Cox[1,3,4,5], and Channing J. Der[1,3*]

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Abstract: KRAS is mutationally activated in 95% of pancreatic ductal adenocarcinoma (PDAC) patients. Direct KRAS inhibitors are under intense preclinical and clinical development, with two $KRAS^{G12C}$ mutant-selective inhibitors (G12Ci) now approved. However, treatment-associated resistance to KRAS inhibitors has been reported in the clinic highlighting an urgent need to identify novel combination treatment strategies. To that end, we performed a CRISPR/Cas9 loss-of-function screen using a library targeting ~2,500 druggable genes. We identified multiple genes that modulated resistance or sensitivity to a pan-RAS inhibitor, including genes identified in patients who relapsed on G12Ci treatment (RB1, PTEN, KEAP1). We further applied an siRNA validation screen on ~40 sensitizer genes and validated 70% of hits, including an mTORC1 subunit Raptor, epigenetic regulator HDAC3, DNA damage repair protein PARP3, and anti-apoptotic protein MCL1. We then selected PRMT5, a protein arginine methyltransferase, to assess as a novel sensitizer to direct RAS inhibitors. We found that suppression of PRMT5 activity using two distinct clinical candidate small molecule inhibitors (JNJ-64619178 and GSK3326595) demonstrated single agent activity and further sensitized PDAC cells to a pan-RAS inhibitor in short-term and long-term growth assays. We next assessed a mechanistically distinct clinical candidate PRMT5 inhibitor, MRTX1719, that is selective for *MTAP*-deleted tumors, which is deleted in ~25% of PDAC patients. We determined that MRTX1719 exhibited low nanomolar GI_{50} activities in MTAP-deficient but not MTAP wild-type KRAS-mutant cell lines. We also found that combination treatment with MRTX1719 and mutant-selective KRAS inhibitors (G12Ci and G12Di) synergistically suppressed the growth of KRAS-mutant PDAC cells. Our ongoing studies are evaluating the consequences of co-targeting PRMT5 and KRAS on cancer cell signaling pathways and gene expression changes in PDAC. In summary, our data support concurrent inhibition of PRMT5 and KRAS as a promising therapeutic strategy for KRAS-mutant pancreatic cancer.

Poster# A016

Praneet Kaur Sandhu, PhD
Postdoc, Microbiology and Immunology, Blossom Damania, Basic Science

Title: DDX5 and DDX17 recruit Brg1 to facilitate lytic reactivation of Kaposi's sarcoma-associated herpesvirus

Authors: Sandhu Praneet Kaur, Damania Blossom

Abstract: DDX5 and DDX17 recruit Brg1 to facilitate lytic reactivation of Kaposi's sarcoma-associated herpesvirus Kaposi's sarcoma-associated herpesvirus (KSHV) is an oncogenic gammaherpesvirus that causes diseases such as Kaposi's sarcoma, primary effusion lymphoma (PEL) and multi-centric Castleman's disease. Kaposi's sarcoma is the most common cancer in HIV-infected individuals. KSHV exhibits two phases of infection in the host: (i) latency, which is a quiescent phase with limited gene expression and (ii) lytic replication, which is an active phase with expression of all viral genes and production of infectious virions. The virus can switch from latency to replication through a process called lytic reactivation. Importantly, KSHV expresses viral proteins that interact with host proteins to modulate cellular processes and create an environment conducive for the viral lifecycle. Given that these viral proteins contribute to KSHV-associated cancers, it is important to identify the host binding partners to elucidate how these viral proteins function. KSHV encoded ORF36 is a viral protein kinase (vPK) that acts as a multifunctional protein and has roles in regulating protein synthesis, angiogenesis, immune evasion, and the DNA damage response. To fully understand vPK's functions, we previously performed a mass spectrometry screen and identified DDX17 and its paralog DDX5 as interacting partners of vPK. The goal of the present study was to characterize the interaction between DDX17, DDX5 and vPK, and determine if the DDX proteins were important for virus infection and replication. First, we confirmed the interaction between vPK, DDX5 and DDX17 using co-immunoprecipitation experiments. Next, using siRNA to deplete DDX5 and DDX17 either singly or in combination, we observed reduced expression of KSHV lytic proteins, decreased gene expression of KSHV lytic genes and lower yield of progeny virions when both proteins were knocked down in either epithelial or B cell lines. These results suggest that DDX5 and DDX17 are required for efficient KSHV lytic replication. Subsequently, we observed that DDX5 and DDX17 were present at the promoter of the key gene that is required for lytic reactivation of KSHV called replication and transcription activator (RTA), and that vPK is capable of binding to the RTA promoter. Additionally, we found that upon depletion of DDX5 and DDX17, there was reduced occupancy of Brg1, a chromatin remodeler, at the RTA promoter. Finally, Brg1 inhibitor treatment results in less lytic reactivation in both epithelial and B cell lines. Taken together, these results suggest that DDX5 and DDX17 interact with vPK and regulate the recruitment of Brg1 to the RTA promoter to drive lytic reactivation of KSHV. This work highlights how vPK interacts with several host DDX proteins to promote viral replication and thus presents a new potential target for therapeutic intervention.

Poster# A017

Brianna Taffe, MPH
Graduate Student, Epidemiology, Sarah Nyante; Melissa Troester; Mya Roberson; Lisa Spees, Cancer Control Education Program, Population Science (Public Health)

Title: Examining associations between quantitative breast density and recall for additional imaging in a community-based breast imaging registry

Authors: Brianna D. Taffe, MPH[1,2,3]; Louise Henderson, PhD[2,3]; Cherie M. Kuzmiak, DO, FACR, FSBI [2,3]; Ley Killeya-Jones, PhD[3]; Sarah J. Nyante, PhD[2,3]
[1]University of North Carolina (UNC) Gillings School of Global Public Health, Chapel Hill, NC, United States; [2]UNC Lineberger Comprehensive Cancer Center; [3]UNC Department of Radiology

Background: Women with screening mammograms that are interpreted as abnormal are recalled for additional imaging. Prior studies have examined associations between being recalled and qualitative measures of breast density, but few have used objective quantitative density measures. This study evaluated the association between quantitative density and risk of being recalled after a screening mammogram.
Methods: We sampled women assigned an abnormal screening mammogram assessment (BI-RADS 0) and compared them to a random sample of women with a normal or benign assessment (BI-RADS 1 or 2) at 6 Carolina Mammography Registry sites between 2017-2018. Fibroglandular volume was measured from full-field digital mammograms using Volpara, and dense area was measured using the Laboratory for Individualized Breast Radiodensity Assessment (LIBRA). Unconditional logistic regression was used to estimate the risk of recall and inverse probability of sampling weights were used to account for participant selection. Age, menopausal status,

and receipt of prior mammogram were identified as potential confounders and adjusted for in multivariable models.
Results: 1,068 women aged 33-86 years (Mean=57.5, SD=11.1) were included in this study. 72% identified as White, 18% Black, 3% Asian, and 6% Other race. 6% identified as Hispanic and 70% were postmenopausal. Dense area and fibroglandular volume were moderately correlated (R=0.40). Recalled women had greater amounts of dense breast tissue compared to the comparison group (Recalled: mean dense area 25.34 cm^2 [SD=24.9], mean fibroglandular volume 53.8cm^3 [SD=29.7] vs. non-recalled: mean dense area 23.9 cm^2 [SD=25.5], mean fibroglandular volume 50.7 cm^3 [SD=26.7]). Fibroglandular volume and dense area were positively associated with being recalled, with unadjusted odds ratios (OR) of 1.27 (95% CI: 1.08, 1.49; p<0.01) and 1.09 (95% CI: 1.01, 1.18; p=0.03), respectively, and adjusted ORs of 1.06 (95% CI: 0.89, 1.26; p=0.53) and 1.03 (95% CI: 0.95, 1.11; p=0.54), respectively.
Conclusion: Breast fibroglandular volume and dense area were associated with being recalled following screening, but associations were attenuated after adjusting for covariates. Quantitative breast density measures are not an effective predictor of recall risk.
Clinical Relevance: Understanding factors associated with recall will help with development of strategies to reduce unnecessary recall of women with non-cancerous abnormal screening results.

4:00-4:45pm
Poster Session (B)
Chancellor's Ballroom

Poster# B001
Alexander Ross Hurley, PhD, MPH
Postdoc, Health Behavior, Deborah Tate, Carmina Valle, Cancer Health Disparities Training Program
Title: Content analysis of young adult cancer survivor peer conversations within a closed mHealth intervention social media group over 6 months
Authors: Lex Hurley, Ph.D., MPH, University of North Carolina at Chapel Hill, Department of Health Behavior
Carmina G. Valle, Ph.D., MPH, University of North Carolina at Chapel Hill, Department of Nutrition, Lineberger Comprehensive Cancer Center
Background: Young adult cancer survivors (YACS) are an understudied population at increased risk for multiple chronic diseases. A majority do not adhere to recommended physical activity (PA) guidelines for survivors to lower risk of such morbidities, and few programs are specialized to meet this vulnerable population's unique needs. IMPACT was a 12-month randomized trial of an mHealth intervention designed to increase PA among YACS (N = 280) compared with a self-help group. The intervention group received adaptive goal setting, Fitbit activity trackers, tailored feedback, text messages, and up to 5 prompts each week posted into a private Facebook group by study staff to promote engagement. Conversely the self-help comparison group only received the Fitbit activity trackers and a separate private Facebook group which received minimal interaction by study staff. Over the course of the study, the self-help group displayed comparable levels of conversation activity on their Facebook wall relative to the moderated intervention group. This secondary analysis seeks to understand and document the types of peer-to-peer interactions among YACS within a closed Facebook group.
Methods: Facebook wall activity for both groups was manually recorded and coded by study staff weekly. This analysis used a subsample of the first 6 months (26 weeks) of post and comment data from approximately n = 78 participants on the basis that mHealth participation and engagement tends to decrease quickly after 6 months. This analysis represents a conventional content analysis using a constructivist epistemology, with a codebook iteratively developed over three waves of analysis to best ensure all content was appropriately identified among user posts and comments.
Results: Discussions mostly aligned with the focus of the study to enhance physical activity, with most conversations relating to social support, physical activity, Fitbits, and cancer specific topics. Participants were often forthcoming about sensitive health issues in their group introductions including diagnoses, chemotherapy, medications, and struggles post-cancer diagnosis, such as frustrations with physical weakness, lack of energy, and weight gain during chemotherapy. Participants displayed high levels of emotional and informational social support; creating a safe, empathetic environment for users to share positive and negative life experiences, sympathies, and motivation, as well as recommendations regarding various medications, oncologists, and YACS events. Users with

shared or similar diagnoses seemed more inclined to share social support among each other; sometimes using humorous terms such as “lymphomies” and “cell mates”. Soon after the trial began, participants began a thread sharing emails to add Fitbit friends list information amongst themselves for mutual encouragement and accountability to increase their exercise levels, and often discussed positive feelings of motivation from the group and seeing each other’s activity levels in their Fitbit friends lists. In contrast, some threads described Fitbit lists and activities with non-cancer survivors as demotivating and mentioned withdrawing from them due to frustrations and damaging effects on self-esteem. This sense of othering from non-cancer survivors, a separation of identities before and after diagnosis, and need to establish new identities for themselves were discussed across several threads. Such comments were consistently met with empathy, encouragement, and personal anecdotes of struggles in display of solidarity. Over time, user conversation frequency on the Facebook page decreased, with new members enrolled via rolling recruitment forwarded to old threads of Fitbit friends list information and other conversation topics by more senior members, and most new posts relating to Fitbit issues and troubleshooting advice by the end of 6 months.

Discussion: This analysis represents a glimpse into the camaraderie and overall positive experiences YACS displayed in posts and comments within a private Facebook group in the context of a randomized trial of an mHealth intervention. Generally, participants shared motivation, high social support, and resources to promote physical activity and health without direction from study staff. Future planned analyses for this data involve expansion into the full 12-month duration of the self-help group, then content analysis and comparison to conversations in the intervention group to determine if the types of conversations substantially differed between the two groups, and use all resulting interpretations to inform tailoring capabilities for future YACS mHealth interventions.

Poster# B002

Dalia Fleifel, BSc

Graduate Student, Biochemistry and Biophysics, Jeannette Gowen Cook, Basic Science

Title: Racing against time: c-Myc overproduction accelerates origin licensing in a short G1 phase.

Authors: Dalia Fleifel[1], Sidra Qayyum[1], Patricia C. Rodríguez-Rodríguez[1], Jeanette G. Cook[1]

[1]University of North Carolina at Chapel Hill, Biochemistry and Biophysics, Chapel Hill, NC

Abstract: Origin licensing is a tightly regulated process that occurs in G1 phase where MCM helicases are loaded onto DNA to “license” multiple sites for DNA replication in S phase. Licensing must occur only in G1, whereas origin firing must occur only in S phase. Thus, G1 is the only window available to license enough origins before entering S phase. Insufficient licensing in G1 leads to incomplete replication and sensitizes cells to DNA damage in S phase, which results in genome instability.

The origin licensing rate is defined as the speed of MCM loading throughout the nucleus in G1 phase. Notably, G1 lengths vary greatly among different cell types, and licensing rates together with G1 length determine the amount of loaded MCMs. Thus, the rate must be tightly coordinated with G1 length to ensure enough loaded MCMs before S phase begins i.e.: a short G1 needs to be counterbalanced by rapid licensing. Our goal is to identify factors that control licensing rates in proliferating cells while maintaining their genome stability. We and others have shown that the G1 in iPSCs is very short, yet they have rapid licensing and can still load as many MCMs as cells with long G1 phases. Notably, a cocktail of Oct4, Klf4, c-Myc, and Sox2 (OKMS) factors can reprogram differentiated cells that have long G1 phases and slow licensing into induced Pluripotent Stem Cells (iPSCs) that have very short G1 phases and fast licensing.

c-Myc is a central regulator of cellular proliferation: it plays a dual role in iPSCs generation as well as cancer transformation. We hypothesize that c-Myc accelerates origin licensing in G1 phase through transcriptional and/or epigenetic mechanisms to establish rapid cellular proliferation. Using single cell quantitative flow cytometry, we recently discovered that c-Myc overproduction in non-transformed epithelial cells shortens the G1 phase and accelerates origin licensing in G1 phase. We found that c-Myc overproduction induces Cdt1, an essential licensing factor, on the mRNA and protein levels. Interestingly, L-Myc, which is another member of the Myc oncoprotein family, elicits a significantly weaker effect on origin licensing and G1 length, compared to c-Myc. Moreover, c-Myc evicts the linker histone H1 and induces global hyperacetylation, which is known to increase chromatin accessibility and facilitate MCM loading. We also discovered that the Myc box-II (MB-II) domain mediates the rapid origin licensing phenotype through the downstream histone acetyl transferase, GCN5. Identifying c-Myc downstream pathways that control origin licensing dynamics will allow us to manipulate origin licensing and cellular proliferation rates in Myc-driven cancers, which might sensitize them to DNA damaging agents.

Poster# B003

Eman Metwally, MD-PhD, MSCR

Postdoc, Epidemiology-Gilling, Caroline Thompson, Population and Translational Science

Title: Emergency Diagnosis of Lung Cancer Among Patients with Chronic Obstructive Pulmonary Disease in The United States

Authors: Metwally EM[1,2], M. Bradley Drummond[3], Sharon Peacock Hinton[1], Caroline A. Thompson. [1,2,4]

Authors Affiliations:

[1] Department of Epidemiology, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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[4] Center for Health Promotion and Disease Prevention, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Background: Diagnosis of lung cancer during acute inpatient hospitalization after emergency department visit (heretofore "Emergency diagnosis of lung cancer" (EDLC)) has been associated with late-stage diagnosis and poorer survival, especially among patients with multimorbidity and disadvantaged racial and socioeconomic backgrounds. COPD is a common comorbidity among patients with lung cancer and is itself a frequent cause of emergency department visits.

Objectives: We sought to characterize prevalence, sociodemographic, clinical, and surgical treatment of emergency vs. non-emergency diagnosed lung cancer among patients with comorbid COPD. We quantified the association between emergency diagnosis of lung cancer and COPD, overall and by race and socioeconomic status (SES). Further, we quantified this association among patients with COPD with versus without acute exacerbation (AECOPD).

Methods: We conducted a secondary data analysis using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) linked to Medicare database including Medicare beneficiaries aged 66+ years with primary invasive lung cancer diagnosed from 2008 to 2017 who were alive at the time of lung cancer diagnosis and had continuous Medicare coverage from 12 months prior to 3 months after lung cancer diagnosis, or until death. **Exposure:** Comorbid COPD diagnosis was determined using ICD-9, ICD-10 diagnosis codes in Medicare claims during the 12 months prior to 3 months after lung cancer diagnosis. **Outcome:** Emergency diagnosis was defined as diagnosis of lung cancer during acute inpatient hospitalization following emergency department visit. **Statistical analysis:** We used generalized linear models to estimate adjusted absolute (prevalence difference) and relative (prevalence ratio) association with emergency diagnosis of lung cancer.

Results: Among 185,405 Medicare beneficiaries with lung cancer, 131,230 (70.8%) had COPD, of them 33,707 (25.7%) had emergency diagnosis of their lung cancer. Among patients with comorbid COPD, those with versus without emergency diagnosis of lung cancer were more likely to be non-Hispanic Black, Hispanic, and had lower census-tract SES. Clinically, they had more comorbidities especially diabetes, and congestive heart failure, were frailer, had more small cell lung cancer, more late-stage cancer, and less primary surgical treatment of lung cancer. We observed a positive association between COPD and emergency diagnosis of lung cancer that persisted after adjusting for age, sex, year of lung cancer diagnosis, and SEER registry region (prevalence ratio= 1.28, 95% CI= 1.25 to 1.31). Among patients with comorbid COPD, there was a positive association between AECOPD and emergency diagnosis of lung cancer (prevalence ratio= 1.76, 95% CI= 1.71 to 1.80). These associations were stronger for patients with non-Hispanic White (vs. NHB and Hispanic) race/ ethnicity, and for patients with highest (vs. Lowest) SES.

Conclusion: Approximately one out of four lung cancer diagnoses occur during acute inpatient hospitalization following emergency department visit among elderly patients in the US. Patients with versus without COPD are at higher risk of emergency diagnosis of lung cancer and its poor cancer outcomes (late-stage diagnosis and less surgical treatment). Beyond established risk factors for EDLC, AECOPD is a novel and important risk factor we identified which should be incorporated into screening protocols of lung cancer detection.

Poster# B004

Genevieve Mullins, PhD

Postdoc, LCCC/Microbiology, Justin Milner, Basic Science

Title: CD8 T cell exhaustion is dynamically controlled by the chromatin regulatory factor BRD4

Authors: Genevieve N. Mullins[1], Jarred M. Green[1], William D. Green[1], Anup Dey[2], Keiko Ozato[2], and J. Justin Milner[1]

[1]University of North Carolina, Chapel Hill, Lineberger Cancer Center, [2]NICHD

Abstract: In the context of chronic viral infections and cancer, the protective potential of CD8 T lymphocytes is often dramatically blunted and characterized by a functionally exhausted cell state. T cell exhaustion contributes to pathogen persistence and can limit responsiveness to promising immunotherapy strategies. Therefore, defining the signals controlling the development and maintenance of an exhausted T cell state has critical implications for global public health. While it has become apparent that T cell exhaustion is a transcriptionally and epigenetically driven process, critical epigenetic mechanisms mediating T cell exhaustion remain unresolved. To this end, we sought to define how the 'chromatin reader' BRD4 controls an exhausted state in a CD8 T cell-intrinsic manner during chronic viral infection. Utilizing inducible deletion mouse models and RNAi, we found that BRD4 is a critical regulator of T cell differentiation and function. BRD4 was essential for driving a terminally exhausted CD8 T cell state. Mechanistically, BRD4 was found to bind near and modulate expression of key genes that influence T cell differentiation and exhaustion. Finally, small molecule inhibition of BRD4 was seen to reverse a terminally exhausted cell state. These findings provide insights into the epigenetic underpinnings of T cell exhaustion and have important implications for enhancing immunotherapy efficacy.

Poster# B005

Ilona Fridman, PhD

Postdoc, LCCC, Jennifer Elston Lafata, Cancer Care Quality Training Program, Population Science - Public Health

Title: Preferences for electronic modes of communication among older primary care patients: a cross-sectional survey

Objective: Health information delivered via daily modes of communication such as email, text, or telephone has been shown to support improved health behavior and outcomes. While different modes of communication beyond clinical visits have proven successful for patient outcomes, preferences for communication modes have not been comprehensively studied among older primary care patients. We addressed this gap by assessing patient preferences for receiving cancer screening and other information from their doctor's office. We explored stated preferences by communication modes through the lens of social determinants of health (SDOH) to gauge acceptability and equity implications for future interventions.

Methods: A cross-sectional survey was mailed to primary care patients aged 45-75 years, in 2020-21. The survey assessed respondents' use of telephones, computers, or tablets in daily life and their preferred modes of communication for different types of health information, including educational materials about cancer screening, tips for taking prescription medication, and protection from respiratory diseases from their doctor's office. Respondents indicated their willingness to receive messages from their doctor's office via each of the provided modes of communication, including telephone, text, email, online patient portal, website, and social media. They reported on a 5-point Likert scale that ranged from "unwilling" to "willing." We present the percentage of respondents who indicated that they were "willing" to receive information via specific electronic mode. Chi-square tests were used to compare participants' willingness by social characteristics.

Results: In total, 133 people completed the survey with a response rate of 27%. The average age of respondents was 64 years; 63% of respondents were female; 83% were White, 16% were Black, and 1% were Asian. In total, 58% reported having a bachelor's degree or higher; 20% resided in rural areas, 29% in suburban areas, 39% in a town, and 12% in a city. The majority, 57%, reported being comfortable with their income. Preferences of respondents for electronic communication about cancer screening were distributed as follows: 75% of respondents were willing to

receive information from their doctor's office via their patient portal, 74% via email, 56% via text, 45% via the hospital website, 38% via telephone, and 11% via social media. About 5% of respondents were unwilling to receive any communication by electronic mode. Preferences were distributed similarly for other types of information. Respondents reporting less income and less education consistently preferred receiving telephone calls relative to other communication modes.

Conclusions: To optimize health communication and reach a socioeconomically diverse population, telephone calls should be added to electronic communication, especially for people with less income and education. Further research needs to identify the underlying reasons for the observed differences and how best to ensure that socioeconomically diverse groups of older adults can access reliable health information and healthcare services.

Poster# B006

Jessica A. Stewart, MS, PhD

Postdoc, Microbiology Immunology, Blossom Damania, UNC Infectious Diseases Pathogenesis Research Training Program, Basic Science

Title: Using the natural product Withaferin A as a prevention therapy for EBV lymphomagenesis

Authors: Jessica A. Stewart, Blossom Damania

Abstract: Epstein Barr virus (EBV) is the etiological agent for many aggressive B cell cancers such as Burkitt's lymphoma (BL), diffuse-large B cell lymphoma (DLBCL), post-transplant lymphoproliferative disorder (PTLD), and Hodgkin's lymphoma. EBV has the highest seroprevalence of any virus infecting ~90% of the world population. For most healthy individuals the virus remains dormant and undetectable. However, children of sub- Saharan Africa have a high incidence of EBV-positive BL. This endemic BL (eBL) is associated with *Plasmodium falciparum* malaria and accounts for 50-75% of child cancers in some countries. Moreover, patients with weakened immune systems are more likely to develop EBV-related complications. Thus, this issue requires urgency and treatments that address not only the current state of the disease but also preventative measures to spare these patients from extensive chemotherapy. EBV infection of B cells *in vitro* and *in vivo* leads to constitutive CD40 signaling, activating the noncanonical NF-κB pathway and promoting lymphomagenesis. This CD40 signaling is critical for promoting B cell transformation and the survival of infected cells. Therefore, targeting and suppressing this pathway may be an effective strategy in preventing EBV lymphomagenesis in immunocompromised patients. Withaferin A (WA) is a natural product isolated from Ashwagandha that has been shown to inhibit activation of the NF-κB pathway in diffuse-large B cell lymphomas and many other solid tumors. We tested this compound on EBV-positive and EBV-negative B cell lines and observed a more potent inhibition in viral infected cells. We have also determined that WA can prevent EBV B cell lymphomagenesis *in vitro* and specifically suppresses the CD40 ligand and interleukin-4 (IL-4) stimulatory pathway. Thus, WA may be useful in treating and preventing EBV-positive B cell malignancies.

Poster# B007

Jonathan DeLiberty

Graduate Student, Pharmacology, Drs. Kirsten Bryant & Channing Der, Clinical or Translational Research

Title: Combined MEK and PIKfyve inhibition therapeutically targets autophagic dependence in pancreatic ductal adenocarcinoma

Authors: Jonathan M. DeLiberty[1], Mallory K. Roach[1], Scott Bang, Noah L. Pieper[2], Kristina Drizyte-Miller[2], Elyse G. Schechter[2], Runying Yang[2], Channing J. Der[1,2], Adrienne D. Cox[1,2,3], Clint A. Stalnecker[1], John P. Morris 4th[1,2] Kirsten L. Bryant[1,2]

[1]Department of Pharmacology, [2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, [3]Department of Radiation and Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is characterized by KRAS- and autophagy-dependent growth. We and others recently demonstrated that inhibition of KRAS signaling through targeting the RAF-MEK- ERK kinase cascade resulted in further reliance on autophagy. Targeting this increased reliance on autophagy with the autophagy inhibitor hydroxychloroquine (HCQ)/chloroquine (CQ) together with MEK or ERK inhibition (MEKi, ERKi) synergistically blocked PDAC growth. These findings provided rationale for our initiation of Phase I/II clinical trials

evaluating the combination of MEKi (binimetinib; NCT04132505) or ERKi (LY3214996; NCT04386057) with HCQ in PDAC. However, a limitation of this approach is that HCQ/CQ are not specific or potent autophagy inhibitors. To this end, we performed a CRISPR-Cas9 mediated genetic loss-of-function screen in PDAC cells to identify other targetable mediators of autophagy.
We identified PIKfyve, a lipid kinase critical for the recycling dynamics of lysosomes, as an essential autophagy-related gene in PDAC cells. PIKfyve inhibition by the clinically tested inhibitor apilimod resulted in potent reduction of autophagic flux and growth. Importantly, PIKfyve inhibition prevented the increased autophagic flux we observed when we inhibited MEK with the clinical stage MEKi mirdametinib. As a result, co- targeting MEK and PIKfyve led to synergistic impairment of PDAC cell proliferation. Similar results were observed following dual inhibition of KRAS and PIKfyve. We found the synergistic growth inhibition was caused by an induction of apoptosis unique to combination treatment. We then tested the combination of MEKi and PIKfyvei in patient derived PDAC organoids and observed a robust synergistic reduction in viability. *In vivo* studies are currently underway to determine the efficacy of single agent PIKfyve inhibition, as well as the efficacy of combined MEK and PIKfyve inhibition in orthotopic mouse models of PDAC. These findings implicate PIKfyve as an effective anti-autophagy target when paired with RAS or ERK-MAPK pathway inhibition in pre-clinical models of pancreatic cancer.

Informational Poster
Kaitlin Smith, MLS, Program Manager, Relational Leadership @ Carolina
Madeline Neal, Director of Special Programs for Interprofessional Education and Practice
Relational Leadership
Relational Leadership @ Carolina is an interprofessional, cross-generational program of the UNC-CH Office of Interprofessional Practice and Education (IPEP) that teaches participants how to fully realize the breadth of their human interactions — with students, patients, colleagues, or decision makers— to achieve true connection, common vision, and interdependent action.

Poster# B008
Kanishk Jain, PhD
Postdoc, Biochemistry and Biophysics, Brian D. Strahl, Basic Science
Title: Understanding the role of PHRF1 in transcriptional regulation and DNA damage response
Authors: Kanishk Jain[1,2], Pata-Eting Kougnassoukou Tchara[3], Aman B. Mengistalem[1], Aidan Holland[1], Christopher N. Bowman[1], Spencer W. Cooke[1] Matthew Marunde[4], Jon Burg[4], Krzysztof Krajewski[1], Michael-Christopher Keogh[4], Jean-Phillipe Lambert[3], and Brian D. Strahl[1,2]
[1]Department of Biochemistry and Biophysics,
[2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC;
[3]Department of Molecular Medicine, Université Laval, Quebec, Canada,
[4] EpiCypher, Inc.
Abstract: Plant homeodomain (PHD) fingers are effectors or "readers" of histone posttranslational modifications (PTMs). Specifically, most PHDs studied to date recognize and bind to unmodified and methylated states of histone H3 K4. Given that there are over 100 PHD finger containing proteins in humans and many of them have biological implications in disease with little understanding of how they function, we have set out to explore the histone binding capabilities of one such protein—PHD and RING finger containing protein 1 (PHRF1). PHRF1, a hitherto relatively uncharacterized protein, contains a PHD finger and is reported to regulator of tumorigenesis in breast and lung cancers. Using biochemical approaches such as histone peptide arrays and peptide pulldown assays, we have found PHRF1 to be robust binder of histone H3, specifically at the N-terminus. Furthermore, site-directed mutagenesis of residue P221 has revealed a critical moiety in mediating PHRF1-histone H3 interactions. RNA-seq and proteomic analysis has also revealed PHRF1 to be involved in transcriptional and RNA-splicing regulation. Finally, ongoing studies have shown ΔPHRF1 cells to be sensitive to DNA damage, implicating PHRF1 in the DNA damage response.

Poster# B009
Lauren Bates-Fraser
Graduate Student, Department of Allied Health Science/ Cancer Care Quality Training Program, Exercise Oncology Lab/ Erik Hanson, Cancer Care Quality Training Program, Population Science (Public Health)

Title: Detecting Cardiovascular Disease Risk in Early-Stage Endometrial Cancer Survivors: Preliminary Evidence of Pulse Wave Velocity and Social Vulnerability Index

Authors: Lauren C. Bates-Fraser[1, 2, 3], Victoria Bae-Jump[2, 4], Lee Stoner[1, 3, 5], and Erik D. Hanson[1, 2, 3]
1. Human Movement Science Curriculum, Department of Allied Health Science, University of North Carolina at Chapel Hill
2. Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill
3. Department of Exercise and Sport Science, University of North Carolina at Chapel Hill
4. Division of Gynecology Oncology, University of North Carolina at Chapel Hill
5. Department of Epidemiology, University of North Carolina at Chapel Hill

Background: Endometrial cancer survivors (ECS) experience high rates of cardiovascular disease (CVD) likely due to lifestyle and social-environmental factors, including high obesity rates up to 60%. Early detection of CVD is crucial in order to intervene; however, strategies to identify ECS most at risk for CVD are currently lacking. The gold-standard methodology to non-invasively measure CVD is pulse wave velocity (PWV), and one way to identify social-environmental susceptibility is the Centers for Disease Control social vulnerability index (SVI).
Purpose: Therefore, the purpose of this study is to investigate (1) CVD risk in stage 1 ECS using PWV and (2) the social-environmental influence on CVD risk using SVI.
Methods: Stage 1 ECS who were 1-12 months post-treatment, with a BMI ≥ 25.0 kg/m^2, age 50-80 years, and English speaking were recruited in the gynecology-oncology clinic. Oscillometric PWV was measured in a supine position via Mobil-O-Graph. Body composition [body fat percentage (%)] was measured via Bioelectrical Impedance Analysis. Participant zip code was used to determine SVI of their county of residence. SVI is defined as low-medium (0.00-0.49), medium-high (0.50-0.69), and high (0.70-1.00). Linear regression was used to compare PWV and SVI.
Results: Seventeen ECS (65% White, 25% Black, 5% Asian, 5% American Indian, 64 ± 7 years old, 6 ± 4 months post-treatment, 44 ± 6% body fat) participated in the study. Participants resided in counties with low-medium (18%), medium-high (24%), and high (58%) SVI and PWV was measured as 8.2 ± 0.8 m/s, 9.1 ± 0.8 m/s, and 9.7 ± 1.0 m/s respectively. The overall regression was not statistically significant ($R=0.38$, $R^2=0.14$, $F=1.15$, $p=0.34$).
Discussion: Overall, PWV was elevated in ECS residing in counties with medium-high and high SVI categories compared to normative data. PWV can be used to non-invasively measure CVD risk in clinic in early-stage ECS. Despite failing to reach statistical significance, a 1.0 m/s change is considered to be a clinically meaningful difference in PWV. Therefore, ECS residing in counties with high SVI may be at greater CVD risk compared to those living in less vulnerable communities. Further research is needed, including a larger sample size, to identify successful interventions to reduce CVD in ECS most at risk.

Poster# B010

Manshu Li, PhD
Postdoc, BRIC, Zibo Li, Basic Science

Title: Preparation of Radiofluorinated Arene Prosthetic Groups via Organophotoredox Catalyzed Nucleophilic Aromatic Substitution

Authors: Manshu Li, [a] Carla Staton, [a] Xinrui Ma, [a] Weiling Zhao, [a] Liqin Pan, [a] Ben Giglio, [a] Haiden S. Berton, [a] Zhanhong Wu, [a] David A. Nicewicz*[b] and Zibo Li*[a]
[a] Department of Radiology, Biomedical Research Imaging Center, and Lineberger Comprehensive Cancer Center University of North Carolina at Chapel Hill
[b] Department of Chemistry, University of North Carolina at Chapel Hill

Background: The accuracy and sensitivity of Positron Emission Tomography (PET) are determined by the biodistribution properties of the PET agents. Therefore, the development of novel and highly selective PET agents is vital in pushing the frontier of PET imaging. Direct radiolabellings of targeting vectors can produce PET agents, but usually require harsh labelling conditions. This strategy is becoming less useful as the targeting vectors are becoming more structurally complicated and labile. Alternatively, the coupling conditions of radiolabelled prosthetic groups and targeting vectors can be mild to allow the utilization of labile targeting vectors. Radiofluorinated arene prosthetic groups are especially appealing due to higher physiological stabilities. The combination of radiofluorinated arene motifs with highly reactive coupling sites represents the ideal prosthetic groups in PET agent constructions. Unfortunately, the established procedures in the preparation of these ideal prosthetic groups usually employ multi-step radiosyntheses with low efficiency. This bottleneck hindered the

development of novel PET agents. A new one-step efficient strategy in preparing robust radiofluorinated arene prosthetic groups is highly desirable and will contribute to the translational research in PET imaging.
Methods and Results: Organophotoredox catalyzed nucleophilic aromatic substitution (S_NAr) features highly reactive cation intermediates and mild reaction condition. One-step efficient radiosyntheses have been accomplished in the preparations of a series of arene prosthetic groups with important coupling sites, including azide, tetrazine, *N*-succinimidyl ester, and halides. Improved step-economy and overall efficiency demonstrated the advantage over prior procedures. We are also reporting the first synthesis of a new radiofluorinated arene prosthetic group with isocyanate coupling site. Application examples of PET agent constructions with our prosthetic groups demonstrated the practical value of our method. The constructed PET agents showed decent cancer uptake in PET/CT imaging.
Conclusion and Clinical Relevance: Organophotoredox catalyzed S_NAr is an efficient and functional group tolerant strategy in radiofluorinated arene prosthetic group preparations. The improved efficiency in the preparation of these prosthetic groups will benefit the development of new PET agents in translational research, and potentially be adopted in future clinical PET agent preparations.

Poster# B011
Meghan O'Leary, PhD
Postdoc, LCCC, Gita Mody, Cancer Care Quality Training Program, Population Science
Title: Assessing thoracic surgery patients' experiences with and motivations for completing postoperative ePRO monitoring to improve future implementation
Authors: O'Leary MC, Leeman J, Gentry A, Stover AM, Teal R, Vu MB, Carda-Auten J, Mody GN
Background: Electronic patient-reported outcome (ePRO) systems can be used to support postoperative patient care through digital symptom monitoring. We aimed to qualitatively assess patients' experiences with and motivations for completing ePROs following thoracic surgery. The goal is to use our qualitative findings to guide future implementation of ePRO symptom monitoring among thoracic surgery patients through a systems science approach.
Methods: Individual interviews with adult patients who previously underwent major thoracic surgery and monitored their postoperative symptoms via ePROs were conducted by phone and guided by the Capability, Opportunity, Motivation model for behavior change (COM-B). We wanted to understand their experiences completing 10-item symptom surveys up to twice weekly for 2 weeks and then weekly for 2 weeks after returning home, during which clinicians were alerted about concerning symptom burden. Interviews were audio recorded, transcribed verbatim, and four team members used a coding-based content analysis to identify themes. We organized themes using COM-B through team discussion.
Results: Twenty-five patients were interviewed. Participants had a mean age of 58 years, were 56% female, 80% White, and 12% Black, and completed a mean of 5.2 out of 6 possible ePRO surveys. More than half (56%) had a history of lung cancer or another malignancy. With respect to capability, patients reported having the knowledge and skills to complete symptom surveys, though a subset described the physical and emotional energy required. In terms of opportunity, or the physical and social factors contributing to survey completion, participants explained that the ePRO interface and survey format, as well as being asked by their provider, facilitated their completion of the symptom surveys. Motivations included perceived individual benefits – specifically, accompaniment and a deepening connection with providers, care improvement (e.g., symptom management), and self-reflection (e.g., setting expectations, tracking progress) – and the opportunity to improve the larger system (e.g., by improving postoperative care and support for all patients). Factors that inhibited motivation included that the simplicity of the symptom surveys limited their fit to patients' individual experiences, and lack of clarity on how the symptom surveys would be used.
Discussion: Participants identified motivating factors for completing ePRO symptom surveys and described the experience of symptom monitoring as relatively feasible. We are now using process flow diagramming to design changes to implementation of ePRO symptom monitoring following thoracic surgery that address participant feedback. These changes include, for example, integrating process steps focused on patient education about the utility of symptom surveys and establishing expectations for symptom burden during the pre-operative period. Future work should consider how to capture patients' complex health experiences in the symptom surveys.

Poster# B012

Minguk Jo, PhD
Postdoc, LCCC, Gupta Lab (Gaorav Gupta), Basic Science
Title: Mre11 liberates cGAS from nucleosome sequestration during tumorigenesis
Authors: MG. Cho, R.J. Kumar, C-C. Lin, J.A. Boyer, J.A. Shahir, K. Fagan-Solis, D.A. Simpson, C. Fan, C.E. Foster, A.M. Goddard, L.M. Lerner, S.W. Ellington, Q. Wang, Y. Wang, A.Y. Ho, P. Liu, C.M. Perou, Q. Zhang, R.K. McGinty, J.E. Purvis, G.P. Gupta
Abstract: Oncogene-induced replication stress generates endogenous DNA damage that activates cGAS/STING-mediated signaling and tumor suppression1–3. However, the precise mechanism of cGAS activation by endogenous DNA damage remains enigmatic, particularly given that high-affinity histone acidic patch (AP) binding constitutively inhibits cGAS by sterically hindering its activation by double stranded DNA (dsDNA)4–10. Here, we report that the DNA double strand break sensor Mre11 suppresses mammary tumorigenesis through a critical role in regulating cGAS activation. We demonstrate that Mre11-Rad50-Nbn (MRN) complex binding to nucleosome fragments is necessary to displace cGAS from AP-mediated sequestration, enabling its mobilization and activation by dsDNA. Mre11 is thus essential for cGAS activation in response to oncogenic stress, cytosolic dsDNA, and ionizing radiation. Furthermore, we reveal that Mre11-dependent cGAS activation promotes ZBP1/RIPK3/MLKL-mediated necroptosis, which is essential to suppress oncogenic proliferation and breast tumorigenesis. Notably, downregulation of ZBP1 in human triple-negative breast cancer is associated with increased genome instability, immune suppression, and poor patient prognosis. These findings establish Mre11 as a critical mediator that links DNA damage to cGAS activation, leading to tumor suppression through ZBP1-dependent necroptosis.

Informational Poster
Patty Spears, BS, FASCO
Patient Advocate, Translational Science and Health Services, Community Outreach and Engagement
Title: Patients and Community Engagement to Educate Researchers (PEER) Program
Description: Patients and Community Engagement to Educate Researchers (PEER) is a patient-centered partnership between patients, community members and researchers to include the human element into Lineberger cancer research.

Poster# B013
Travis Nelson, PhD
Postdoc, Chemical Biology and Medicinal Chemistry (CBMC), Nate Hathaway, UNC Integrated Translational Oncology Program, Clinical or Translational Research
Title: Targeted modulation of *TP53* expression with a small molecule epigenetic modifier & CRISPR/Cas9 to induce apoptosis
Authors: Nelson TJ, Kemper RM, Chiarella AM, Crona DJ, Hathaway NA
Abstract: Epigenetic dysregulation of gene expression is a common driver of a variety of human diseases, including cancer. Post-translational modifications of chromatin can result in abnormal regulation of key genes, leading to pathogenesis and a suppression of normal function. Of particular concern is the gene *TP53* and the tumor suppressing protein it encodes, p53. This transcription factor regulates signaling pathways that are associated with the maintenance of cellular homeostasis, response to cellular stresses, and tumor suppression. As such, *TP53* is mutated or epigenetically downregulated in many cancers and therefore makes for an attractive target for therapeutic upregulation. Current approaches towards epigenetic regulation largely rely small molecule drugs or large CRISPR/Cas9-based fusion proteins, which provide either a dose-dependent response or a gene-specific response, but not both. Recent work in our lab has focused on combining these two features to utilize the best of both worlds. We have engineered a system that combines a nuclease-deficient of CRISPR/Cas9 (dCas9), a guide RNA (gRNA), and a fusion protein containing the FK506 binding protein (FKBP), which links to a two-headed small molecule “chemical epigenetic modifier” (CEM). This final CEM component consists of FK506 linked to a bromodomain inhibitor, and is thus designed to recruit a cell’s endogenous epigenetic activators to a specific gene of interest. Here, we present preliminary work demonstrating that this dCas9-FKBP-CEM system to is capable of epigenetically upregulating *TP53* expression in a variety of cancer cell lines and is capable of inducing a significant shift towards apoptosis in a stomach cancer cell line.

Poster# B014

Xin Zhou, PhD

Postdoc, LCCC, Gianpietro Dotti, Basic Science

Title: CAR-redirected natural killer T cells demonstrate superior antitumor activity to CAR-T cells through multimodal CD1d-dependent mechanisms

Authors: Xin Zhou[1], Ying Wang[2], Zhangqi Dou[1], Gloria Delfanti[3], Rania Tsahouridis[1], Caroline Marie Marnata Pellegry[1], Manuela Zingarelli[1], Gatphan Atassi[1], Mark Woodcock[1], Giulia Casorati[3], Paolo Dellabona[3], William Y Kim[1,4], Barbara Savoldo[1,5], Linjie Guo[2], Ageliki Tsagaratou[1,4], J. Justin Milner[1,6], Leonid S. Metelitsa[2], Gianpietro Dotti[1,6*]

Abstract: Natural killer T (NKTs) cells are a subset of innate-like T cells characterized by CD1d restriction. Human NKTs have been proposed as a novel cell platform for chimeric antigen receptor (CAR) engineering to overcome some of the intrinsic limitations CAR-T cells encounter in solid tumors. We compared in syngeneic models of solid tumors the mode of action of CAR-NKTs versus CAR-T cells (CAR-Ts) and evaluated the interaction of each cell type with an intact immune system. While CAR-NKTs and CAR-Ts demonstrate similar levels of CAR-mediated killing of tumor cells in vitro, CAR-NKTs showed superior in vivo antitumor activity through the activation of CD1d-dependent immune responses in the tumor microenvironment. Specifically, we show that CAR-NKTs eliminate CD1d-expressing M2-like tumor-associated macrophages, promote activation of dendritic cells, and boost antigen cross-presentation, resulting in epitope spreading and activation of endogenous T cell responses against tumor-associated neoantigens. Additionally, we observed that CAR-NKTs co-express PD1 and TIM3 and become functionally exhausted-like in a mouse model with high tumor burden. PD1 blockade significantly increased the antitumor activity of CAR-NKTs in the high tumor burden model. Overall, our results demonstrate the multimodal nature of CAR-NKT antitumor activity in solid tumors, providing rationale for further clinical development of these engineered cells.

Poster# B015

Aaron Hobbs, PhD

Assistant Professor, Department of Cell and Molecular Pharmacology & Experimental Therapeutics
Medical University of South Carolina

Title: KRAS Mutant-Specific Interactions Reveal Mechanisms In Pancreatic Cancer Tumorigenesis And Metabolic Function

Authors: Kamala Sudararaj[1], Rachel Burge[1], Samaneh Saberikashani[2], Lucas Bialousow[1], Amanda Linke[2], Merissa Smith[2], Albert Mao[2], John P. O'Bryan[1,2], Mike Ostrowski[2,3], and G. Aaron Hobbs[1,2]

Affiliations: [1]Department of Cell and Molecular Pharmacology and Experimental Therapeutics; [2]Hollings Cancer Center, [3]Deparment of Biochemistry, Medical University of South Carolina, Charleston, SC 29425

Background and Aims: Mutational activation of the KRAS proto-oncogene is the initiating mutational event in pancreatic ductal adenocarcinoma (PDAC) and ~90% of patients harbor KRAS mutations. PDAC is a disease marred by a 12% five-year overall survival rate, and developing effective therapeutic strategies remains a priority. Accumulating evidence suggests that all KRAS mutations are not created equal. While the $KRAS^{G12R}$ mutation is rare in lung and colorectal cancers (<1%), it is the third most common KRAS mutation in PDAC, accounting for approximately 20% of all cases. Our published data support this mutant as a potent PDAC driver. However, $KRAS^{G12R}$ cannot interact with the lipid kinase PI3Ka, a well-characterized RAS effector necessary for KRAS-driven tumorigenesis. There are four isoforms of PI3-kinases. PI3Ka/b are ubiquitously expressed and PI3Kd/g are considered to be only expressed in blood and immune cells. PI3Ks are negatively regulated by the protein phosphatase PTEN. Previous studies in mice models of cancer have demonstrated that ablation of the KRAS:PI3Ka interaction limits tumorigenesis. Despite the inability of $KRAS^{G12R}$ to activate PI3Ka directly, AKT signaling is robustly activated in $KRAS^{G12R}$-mutant PDAC. The mechanisms that allow the $KRAS^{G12R}$ mutant to overcome the inability to activate PI3K and promote PDAC are unclear.

Methods: We utilized a panel of human PDAC cell lines to probe the role of PI3K isoforms in promoting PDAC proliferation in KRAS-mutant PDAC. Further, we have recently generated a Ptf1a-CRE^{ERT2};$Kras^{LSL-G12R}$ genetically engineered mouse model. We have developed mouse pancreatic organoids and have ectopically expressed mutant PI3K isoforms in these organoids to determine the role of PI3K signaling in promoting tumorigenesis. Further, we have crossed our $Kras^{G12R}$ mouse with $Pten^{fl/fl}$ mice to promote constitutive PI3K signaling and mimic PTEN oxidation

to drive tumorigenesis in a $Kras^{G12R}$ mouse, marking the first time that tumors have been generated in mouse models harboring the $Kras^{G12R}$ mutation.

Results: We recently developed a $Kras^{LSL\text{-}G12R/+}$ genetically engineered mouse model to study $KRAS^{G12R}$ in an in vivo context. Surprisingly, this mouse model does not develop pancreas lesions or tumors. We have uncovered two unique characteristics of human PDAC that we hypothesize allows for the $KRAS^{G12R}$ mutation to produce tumors only in human pancreatic tissue. First, we have found that all four PI3K isoforms are overexpressed in human PDAC, and the PI3Kd and PI3Kg isoforms are specifically upregulated in $KRAS^{G12R}$-mutant PDAC. Second, PTEN is oxidized in PDAC. PTEN oxidation results in an intramolecular disulfide bond, which inhibits the phosphatase activity of PTEN and leads to hyperactivated PI3K signaling. Critically, mouse pancreas tissue only expresses the PI3Ka/b isoforms and PTEN is in the reduced state, demonstrating two significant differences between mouse models and human disease. Additionally, we have determined that PTEN becomes fully oxidized in nutrient-restricted medium (low glucose/glutamine), a common strategy employed to mimic the pancreatic tumor microenvironment in cell culture. Using PTEN oxidation-resistant variants, we demonstrate that $KRAS^{G12R}$-mutant PDAC cell lines are reliant on oxidized (inactivated) PTEN for proliferation. Thus, our data demonstrate that increased PI3K isoform expression, coupled with PTEN oxidation, creates a unique environment that allows $KRAS^{G12R}$ to initiate and promote pancreatic tumorigenesis. To confirm that PTEN inactivation can aid $KRAS^{G12R}$-mediated tumorigenesis in mouse models, we generated at $Kras^{G12R/+}$;$Pten^{fl/fl}$ genetically engineered mouse model, and the results of this model will be presented herein.

Conclusions: Determining how KRAS mutant-specific signaling differentially promotes PDAC tumorigenesis will be critical in developing a complete understanding of tumor initiation as well as response to therapies. We propose that $KRAS^{G12R}$ requires PTEN oxidation (loss of activity, hence PI3K activation) to initiate tumorigenesis. Further, our data suggest that PI3K isoforms may be activated independent of KRAS activity, and reversing PTEN oxidation may serve as a viable therapeutic strategy in these patients. As PTEN oxidation overcomes the need for KRAS to activate PI3K signaling in PDAC, these results indicate that directly targeting KRAS alone will be insufficient at reducing tumor growth in humans and clinically successful therapeutic strategies will have to develop alternative methods to reduce PI3K signaling in addition to directly targeting KRAS activity.

Informational Poster

Alan Marsh, PhD, BSc

Associate Director for UNC Office of Postdoctoral Affairs

Office of the Vice Chancellor for Research

Title: UNC Office of Postdoctoral Affairs (OPA): Centralized Support for All UNC Postdocs, Faculty, & Staff.

Description: The UNC Office of Postdoctoral Affairs (OPA) promotes postdoctoral training at UNC-CH, preparing scholars for successful research careers. OPA works closely with faculty and human resources professionals to provide guidance on postdoctoral recruitment, hiring, and retention, serving as a central resource for postdoc policy, benefits, and grievances. With a professional staff consisting of an interim director, an associate director, two certified career counselors, a program coordinator, and two faculty advisors, OPA serves postdoctoral scholars across all disciplines, schools, and colleges at UNC. OPA also directs the Carolina Postdoctoral Program for Faculty Diversity for the university, with the primary purpose of developing scholars from underrepresented groups for possible tenure-track appointments at Carolina and other research universities.

Poster# B016

Michele Thomas

Graduate Student, Chemical Biology and Medicinal Chemistry, Samantha Pattenden, Clinical or Translational Research

Title: A rapid and simple method for extraction of high-quality chromatin from archived tissues

Authors: Michelle D. Thomas[1], Lauren Sweeney[1], Marjan Mehrab-Mohseni[2], Brian Velasco[2], Nicholas Toomer[1], Paul A. Dayton[2,3], Ian J Davis[3,4,5], and Samantha G. Pattenden[1,3]

[1]Division of Chemical Biology and Medicinal Chemistry, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill; [2]Joint Department of Biomedical Engineering, University of North Carolina at Chapel Hill; [3]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; [4]Department of Genetics, School of Medicine, University of North Carolina at Chapel Hill; [5]Division of Pediatric Hematology-Oncology, Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill.

Abstract: For decades Formalin-Fixed Paraffin Embedded (FFPE) tissue blocks have been a valuable resource for clinical research and for diagnostic applications but are still currently underutilized for epigenetic research. Epigenetics is the study of heritable changes in phenotype, without changes to the underlying DNA sequence. Since DNA templated processes such as transcription and gene silencing are heavily influenced by chromatin accessibility status, disruption of this organization can result in disease. Therefore, “accessible” chromatin is nucleosome-depleted, and nucleosome-rich regions are “inaccessible”. Currently, studying the chromatin landscape has been limited to fresh tissue and cell culture, due to the challenges in capturing and recovery of high-quality chromatin from archived tissues. To overcome this challenge, we developed a technology called nanodroplets, which consist of a lipid shell surrounding a liquid perfluorocarbon core. We demonstrated that nanodroplets efficiently aid in the extraction of intact chromatin from xenograft FFPE tissues during acoustic sonication. We also show that we can isolate high quality chromatin from primary mouse organ and human tumor FFPE tissues using this novel technology. Our results indicate chromatin extracted with our cavitation enhancement reagent can be used in chromatin-based followed by next-generation sequencing. Overall, nanodroplets are a first-in-class technology, providing a fast and simple resource for extracting high-quality chromatin from complex archival tissues for epigenetic research.

4:45-6:00pm

Reception - Refreshments & Oral Presentation/Poster Awards

Chancellor’s Ballroom