THE University of Vermont CANCER CENTER

2025
Scientific Retreat
Abstract Compilation

Anticoagulation Patterns While Undergoing Heparin-Induced Thrombocytopenia Testing

Jessie Caprino, PGY2 Resident Physician
Mentor: Karlyn Martin, MD

Heparin Induced Thrombocytopenia (HIT) requires both clinical and pathologic criteria. Guidelines recommend HIT PF4 antibody testing only for those at intermediate- to high-risk based on the 4Ts score and a non-heparin anticoagulant while awaiting results. Real-world anticoagulation use during HIT evaluation is unknown.

We conducted a retrospective cohort study using inpatient data from four US hospital systems. We included admissions to medical services during which a HIT antibody was tested from 2018-2022. The primary outcome was anticoagulation intensity (none, prophylaxis, therapeutic) on the day after HIT antibody testing (day +1). We used univariate logistic regression to estimate the association of therapeutic anticoagulation on day +1 with various factors, including level of anticoagulation day prior to HIT testing (none, low dose heparin (ie, flush), prophylaxis, therapeutic), platelet count on day of HIT testing (<50, 50-100, 100-150, >150), admitting service (ICU vs non-ICU), and creatinine (Cr <2 vs ≥2).

Of 1202 admissions with HIT antibody testing, patients had a mean age of 61.9 (14.7) years, 52% were male and 59.1% White race (Table). Overall, 609 (50.6%) admissions had no anticoagulation, 416 (34.6%) had therapeutic, and 177 (14.7%) had prophylactic anticoagulation on day +1. Therapeutic anticoagulation on day +1 was associated with therapeutic anticoagulation on day prior to HIT testing (OR 15.40, 95% confidence interval [CI] 10.7,22.12) and ICU admission (OR 1.34; 1.03,1.73). Platelet count <50 (OR 0.56; 0.36,0.87) and being female (OR 0.75; CI 0.59, 0.95) were associated with lower likelihood of therapeutic anticoagulation on day +1.

In a large, diverse cohort of admissions with HIT antibody testing, half of patients were not on therapeutic anticoagulation the day after HIT testing. Whether this is due to inappropriate HIT testing in low-risk individuals or failure to treat intermediate-to-high-risk individuals requires further study.

Shared Experience of Frailty and Social Participation Among Caregiving Dyads

Hyojin Choi, Postdoctoral Fellow
Mentors: Maija Reblin, PhD; Robert Gramling, MD, DSc

Given the concept of linked lives, we can expect that caregivers' social participation can potentially be constrained when the care recipient is frail and needs more care; and care recipients' social participation can be constrained when the caregiver is frail and is less able to support outings. The purpose of this study was to examine how frailty and social participation are interrelated among caregiving dyads and whether this association differs by the health condition (i.e., cancer and dementia) of care recipients. The National Health and Aging Trends Study and the National Survey of Caregiving 2015 and 2017 were utilized. The sample consists of caregiving dyads, including cancer dyads (n=77) and dementia dyads (n=138). Actor-Partner Interdependence models found that in cancer dyads, only an actor effect of frailty was observed for caregivers, indicating that increases in caregivers' frailty reduced their own social participation, but no actor effects were shown for care recipients. Dementia dyads show both actor and partner effects, such that in addition to caregivers' own increased frailty predicting their own lower social engagement, when care recipients' frailty increased, caregivers engaged in fewer social activities. The findings highlight the need for further examination of how caregiving contexts affect dyad's lives.

Oncologic Outcomes for Invasive Squamous Cell Carcinoma with a Clinically Resolved Biopsy Site Managed by Watchful Waiting

Hayden Christensen, Medical Student
Mentor: Melanie Bui, MD, PhD

Cutaneous squamous cell carcinoma (cSCC) constitutes approximately 20% of non-melanoma skin cancers. Occasionally, pathology proven cSCC biopsy sites appear clinically resolved at follow-up. Here, we examine outcomes of clinically resolved cSCCs managed by watchful waiting (WW).

This retrospective cohort included 148 biopsy-proven cSCCs deemed clinically resolved at follow up and managed with WW. Tumors were evaluated for local recurrence, nodal and distant metastasis, and disease-specific death. Participant and tumor characteristics were recorded, and tumors staged per AJCC-8/BWH guidelines.

Among these cases, local recurrence was observed in 1.4% (2/148) with a median follow-up of 35 months. No metastases or cSCC-specific death were observed. Most tumors were less than 1cm (72%), with many located on the head and neck (48%). Most tumors possessed at least one positive margin (83%) and were well differentiated (90%). Two tumors were staged at T2 and 146 at T1.

The recurrence rate of 1.35% in this cohort falls below the 4-5% recurrence rate of surgically treated cSCC. Our report supports WW as an additional management strategy for low risk cSCCs with healed biopsy sites lacking clinical evidence of residual tumor.

Peroxiredoxin 3 is a Key Regulator of Mesothelioma Progression and a Target for Therapeutic Intervention

Victoria Gibson, PhD Candidate
Mentor: Brian Cunniff, PhD

Tumor cells generate increased levels of reactive oxygen species (ROS) to promote growth. To survive, tumor cells must increase antioxidant expression and activity. Peroxiredoxin 3 (PRX3), a mitochondrial matrix hydrogen peroxide (H_2O_2) scavenging enzyme, is overexpressed in cancers, supporting proliferation, apoptosis resistance, and chemotherapy tolerance. RSO-021, a first-in-human covalent inhibitor of PRX3, showed signs of efficacy in a phase 1 trial to treat patients with mesothelioma, warranting transition to phase 2 trials. RSO-021 inhibits PRX3 by crosslinking active site cystines, increasing mitochondrial ROS and inducing tumor cell death. We generated CRISPR/Cas9- PRX3 knockout (KO) mesothelioma cell lines that show significantly reduced proliferation and increased mitochondrial ROS. Seahorse assays showed decreased basal and maximal oxygen consumption in PRX3 KO cells, highlighting PRX3's role in mitochondrial function. PRX3 KO cells failed to form tumors in SCID mice, while control cells resulted in significant tumor burden. RNA sequencing of PRX3 KO cells and patient-derived mesothelioma explants treated with RSO-021 showed reduced expression of epithelial-to-mesenchymal transition (EMT) and TGFβ signaling genes, key pathways in tumor aggressiveness. These findings establish PRX3 as a critical regulator of redox metabolism, mitochondrial function, and tumor progression in mesothelioma, supporting its potential as a therapeutic target in oncology.

Decoding the Link Between Centrosome Dysfunction and Mitotic Infidelity

Matthew Hannaford, PhD, Assistant Professor

Each day over 300 billion cells in the human body are estimated to go through cell division, that must be carefully regulated to ensure that chromosomes are evenly divided. Chromosome segregation is facilitated by the mitotic spindle, where filaments called microtubules pull sister chromosomes apart. Microtubules are organized by organelles called centrosomes. Healthy cells contain two centrosomes, which become located on opposing ends of the mitotic spindle, ensuring that the chromosomes are separated evenly. Cancer cells, however, frequently exhibit more than two centrosomes, centrosomes that are mispositioned through interphase and centrosomes that are abnormally large. Supernumerary centrosomes have been the target of much research, leading to an approved drug for acute myeloid leukemia, however, little is known about the contribution of centrosome position and centrosome size to disease. We use *Drosophila* as a genetic model to investigate the mechanisms regulating centrosome position and size. We have shown that mispositioning centrosomes within a developing epithelium is sufficient to induce error prone mitosis. Furthermore, we have discovered a novel protein interaction regulating centrosome size that when disrupted causes spindle abnormalities in the developing brain. These phenotypes are consistent with errors in chromosome segregation which we are now investigating.

Regulation of APOBEC3A in Breast Cancer

Alyssa Hurley, Graduate Student
Mentor: Steven A Roberts, PhD

APOBEC-associated mutations have been identified in 50% of sequenced human tumors, with APOBEC3A (A3A) implicated as the primary source of mutations in breast cancer cells. However, the mechanisms behind A3A activation and mutagenesis in breast cancers are still unknown. We found that A3A mRNA correlates with A3A protein levels and predicts the amount of APOBEC signature mutations in a panel of breast cancer cell lines, indicating that increased transcription may be one mechanism leading to breast cancer mutagenesis. Through analysis of RNAseq and ATAC-seq data we identified genes that were co-expressed with A3A, in addition to transcription factor binding sites within the A3A promoter region. We altered expression of these genes, as well as Her2 which was previously identified as a potential influencer on A3A. We demonstrate that Her2 can drive A3A expression, and reduction of Rel-A and Bach1 transcription factors negatively regulate A3A. Despite evidence that STAT signaling may be an additional regulatory factor, direct inhibition of STAT signaling had little impact on A3A expression. These findings demonstrate the complexity of A3A transcriptional regulation and identifies multiple factors that may contribute to mutagenesis in breast cancer cells through regulation of A3A.

No Evidence of Residual Disease Observed in 31% of Cutaneous Squamous Cell Carcinoma Biopsy Sites

Caroline Johnston, Medical Student
Mentor: Melanie Bui, MD, PhD

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Background
Cutaneous squamous cell carcinoma and carcinoma *in situ* (cSCC) are routinely treated surgically. However, watchful waiting (WW) for very low-risk cases, defined by no evidence of disease at the healed biopsy site, have low local recurrence rates of 1-4%.[1] This study quantifies the proportion of cSCC without residual disease at follow-up.

Methods
This prospective cohort includes 319 consecutive biopsy-proven cSCC between May 1st and August 31st, 2024. Tumors were evaluated for residual disease at follow-up (residual, no residual, or unable to assess). Treatment plan was recorded.

Results
Of the 319 biopsies, 286 had follow-up. Of these, 31% (n=89) showed no residual disease, 48% (n=136) had evidence of disease, and 21% (n=61) were indeterminate. Among those with no residual disease, 84% (n=75) chose WW, while 16% (n=14) underwent treatment. Average follow-up time occurred 87 days after initial biopsy.

Of those with observable residual disease, 5% (n=7) opted for watchful waiting, while 95% (n=129) received treatment. In the indeterminate group, 7% (n=4) chose watchful waiting, and 93% (n=57) underwent treatment. Among those without follow-up examination, 73% (n=24) chose watchful waiting.

Discussion
Thirty-one percent of cSCC biopsy sites healed with no evidence of residual disease and may be eligible to discuss WW.

References:
1. Boudreaux B, Christensen H, Porter HJ, et al. Oncologic outcomes for invasive squamous cell carcinoma with a clinically resolved biopsy site managed by watchful waiting: A retrospective cohort study. *J Am Acad Dermatol*. 2024. doi:10.1016/j.jaad.2024.11.067

Access to Non-FDA Approved Cancer Therapies for Pediatric Patients at the University of Vermont Medical Center

Margret Joos, Medical Student
Mentor: Jessica Heath, MD

Although groundbreaking advances have been made in pediatric cancer treatment, numerous challenges remain, especially in rural settings. We investigated how social determinants impact patients' ability to access non-FDA approved therapies via retrospective chart review of patients who received chemotherapy between 2013 and 2024. Area deprivation index (ADI), a cumulative score encompassing income, education, employment, and housing quality, was calculated using University of Wisconsin's Neighborhood Atlas Tool, with higher scores (up to 100) indicating increased deprivation. Of 159 patients analyzed, 73 were covered by Medicaid, 44 by private insurers, and 42 by multiple insurers. Average ADI was 52 (SD=22; range 11-97). Average distance (miles) traveled for treatment was 76 (SD=76; range=0.6–336). Patients insured by Medicaid were found to have higher ADI than those with private or multiple insurers. Patients with higher ADI were found to need to travel further for treatment. Significant differences in ADI were not found between protocol types (clinical trial vs. off-study vs. standard of care) or treatment purpose (curative vs. palliative vs. transplant conditioning). Thus, although patients with higher ADI may experience barriers to treatment, they are not being denied access to non-FDA approved therapies – offering both a glimmer of hope and areas for improvement.

Transcription-Associated TOP1-Dependent Mutations in Human Cancer

Vanessa Leandra Lopez, PhD Candidate
Mentor: Steven A Roberts, PhD

Cancer cells typically have elevated rates of mutation, which promotes metastasis, cancer progression, and resistance to cancer therapeutics. Though many forms of DNA damage exist, DNA-protein crosslinks, like Topoisomerase 1 cleavage complexes (TOP1ccs), which form when TOP1 acts on DNA to remove supercoiling during transcription, are especially harmful because of their bulky protein component and targeting to transcribed genic regions. In yeast, TOP1 activity has been shown to contribute to transcription-associated mutagenesis (TAM) and produces a signature of 2-to-5bp deletions at tandem repeats. However, the identification of additional signatures associated with TOP1, the ability of TOP1 poisons to cause the mutations, and the contribution of TOP1ccs to mutagenesis in cancer requires further investigation. To accomplish this aim, we utilized a TOP1 variant, TOP1-T718A, which we demonstrated to increase the generation of TOP1ccs, and a novel mutation reporter in a U2OS-derived cell line with a polycistronic set of genes, allowing the selection of mutations in human cells. TOP1-T718A expression demonstrated increased mutation rates beyond previously documented 2-to-5bp deletions, but also novel larger microhomology-mediated deletions and templated insertions with unknown etiology. These larger Microhomology-mediated deletions and templated insertions mirror reversion mutations in BRCA1/2 that contribute to PARP inhibitor resistance.

“Why Should we all Bundle up, Drive an Hour?”: Connection, Communication, and Convenience in Telehealth Serious Illness Conversations with Rural Cancer Patients

Stasha Medeiros, PhD Candidate
Mentor: Elise Tarbi, PhD, APRN

Authors: Stasha Medeiros, Amelia Haque, Serena Verma, Abhishek Ambati, Maija Reblin, Robert Gramling, & Elise Tarbi

Telehealth can overcome functional, cost, and geographic barriers to attending in-person visits for people living with cancer in rural areas. Yet this medium presents clinicians, patients, and families with a new sensory and relational environment within which to engage in serious illness conversations, including developing foundational connections for effective serious illness communication. We sought to explore the influence of communication features on the experience of connection in telehealth serious illness conversations with rural-dwelling patients with cancer. Using a qualitative descriptive approach, we conducted semi-structured interviews with rural cancer patients (n = 17). Through directed content analysis of study interviews, we identified three emerging insights: 1) patients value the accessibility and convenience of telehealth, despite some sense that connection feels different; 2) patients feel connected to their clinicians when they feel valued, important, and heard; feelings that can be fostered through a variety of communication practices; 3) patients’ experience of connection is impacted by factors such as the underlying patient-clinician relationship, comfort with technology, and the topics being discussed during the appointment. Our study findings help to illustrate that building connection is possible in this setting, and suggest candidate communication features and contextual variables to investigate in future work.

Using a Multipronged Approach to Characterize C-terminal Domain Polybasic Motif STK11 Variants

Gopika Nandagopal, PhD Candidate
Mentors: Paula Deming, PhD; David Seward, MD, PhD

KRAS-driven lung adenocarcinomas (LUADs) with STK11 loss-of-function (LoF) mutations are linked to aggressive tumors, with increased metastasis, and poor survival outcomes. STK11, a serine-threonine kinase, and its LoF impacts many aspects of coordinated cell motility and promotes alterations characteristic of metastasis. In previous work we classified STK11 missense mutations of unknown significance for pathogenicity using a biochemical approach to determine if they retain kinase activity. Here we found that C-terminal domain (CTD) STK11 variants retain kinase function. The CTD, though not catalytic, is essential for STK11 localization to the plasma membrane and cytoskeleton, where it negatively regulates focal adhesion kinase (FAK). Recent literature has shown that the polybasic motif (PBM) within the CTD is key for plasma membrane localization – we therefore reasoned that mutations to this residue would result in impeded STK11 function that cannot be captured by studying kinase activity alone. Indeed, our work shows that STK11 PBM point mutants (R409W, K416E, A417S, K423E), disrupt localization, leading to nuclear sequestration while retaining kinase activity. As an additional measure of STK11 function in these mutants we are looking at their ability to negatively regulate FAK. We demonstrate in KRAS-driven LUAD cells, loss of STK11 leads to elevated FAK activity, as shown by increased pY397-FAK autophosphorylation levels. This approach will be used to similarly query cell lines expressing PBM point mutants for elevated pFAK levels. Additionally, a stable K416E_K423E double mutant cell line is being generated to study the impact of PBM mutations on cell migration, and the TurboID system is being used to identify PBM-dependent STK11 interacting proteins.

The Hexosamine Biosynthetic Pathway Enhances Metastatic Potential upon Glutamine Deprivation in STK11 Null KRAS-Driven Lung Adenocarcinoma

Shannon Prior, PhD Candidate
Mentor: Paula Deming, PhD

Each year there are ~15,000 new US cases of aggressive lung adenocarcinoma (LUAD) driven by concurrent KRAS and STK11 mutations (KS). Given its increased glutamine dependency, KS LUAD has been a candidate for glutaminase inhibitor treatment although clinical efficacy remains unclear. Recently, our group demonstrated pro-oncogenic signaling in KS LUAD cells upon glutamine withdrawal, suggesting adaptation to nutrient stress. We therefore hypothesized that glutamine scarcity induces a pro-metastatic state in KS LUAD. To test this, a cell culture model of KRAS-driven LUAD with and without STK11 (ΔSTK11) was employed. Upon removal of glutamine, ~3-fold more ΔSTK11 cells detached, remained alive and maintained the ability to re-adhere in nutrient replete media. Additionally, glutamine deprivation induced enhanced ameboid-like 3D invasion of ΔSTK11 spheroids. To determine the underlying mechanism(s) of this pro-metastatic shift, we employed heavy nitrogen labeling which revealed an upregulation of the hexosamine biosynthetic pathway (HBP). Treatment with the HBP inhibitor, FR054, reduced 2D and 3D metastatic potential of ΔSTK11 cells upon glutamine deprivation, suggesting its use as a protective shunt. Overall, our data reveal novel insight into the metabolic rewiring of ΔSTK11 cells and provide clinical implication given the consideration of glutaminase inhibitors as a therapeutic approach for KS LUAD.

STK11 Loss of Function in KRAS Driven Lung Adenocarcinoma Promotes Cancer Stemness

Cole Royer, Research Technician
Mentors: Melissa Scheiber, PhD; Paula Deming, PhD

Retrospective patient studies have demonstrated that concurrent oncogenic *KRAS* and *STK11* LoF mutations are associated with metastatic disease, poorer patient survival, and inferior therapeutic response. We hypothesize that STK11 loss in KRAS-driven LUAD enriches the cancer stem cell (CSC) population. CSCs represent a small subset of tumor cells capable of self-renewal, asymmetric division, and tumor initiation. Given their role in metastasis, chemoresistance, and disease progression, CSCs could be key contributors to the aggressiveness observed in KRAS-driven STK11 LoF LUAD. To test this hypothesis, we utilized the KRAS-driven LUAD cell line and an STK11 knockout variant (ΔSTK11) to assess differences in CSC properties. While 2D cultures showed similar CD44 expression, ΔSTK11 spheroids in 3D culture exhibited significantly higher CD44 mRNA. CD44 plays a critical role in maintaining the stem-like properties of cancer cells, however, the precise mechanisms connecting CD44 expression and STK11 remain unclear. To address this, we are investigating transcription factor pathways, including NF-kB and HIPPO, to elucidate their roles in mediating enhanced CD44 expression upon STK11 loss. Using an embryonic zebrafish xenograft model, we aim to characterize CSC function in KRAS-driven STK11 LoF LUAD. Our findings suggest STK11 loss promotes CSC enrichment and metastasis, providing potential therapeutic targets for this aggressive cancer.

Identification of APOBEC3A Protein Interactions through Yeast Two-Hybrid Screen

Dan Schiefen, Undergraduate
Mentor: Steven A Roberts, PhD

My research project revolves around the characterization and identification of APOBEC3A (A3A) protein-protein interactions. A3A is a member of the APOBEC family, a family of cytidine deaminases involved in viral restriction in the innate immune system. Dysregulation of A3A has been found to contribute to mutagenesis through C-to-T and C-to-G single-base substitution patterns, which have been recognized in around 50% of all cancer genomes. My project aims to identify and characterize novel interactors of A3A as they have not been documented in previous research. I have identified interactors through a Yeast Two- Hybrid Screen, and have multiple promising results including TAX1BP1, RNF2, and other immune system proteins. These interactions have been confirmed through additional Yeast Two-Hybrid mating, and I am prepared to move onto further testing. Characterization of these interactions will involve analysis of protein domains of interest and cellular localization patterns based on protein expression levels. Localization testing will be performed using BT474 cancer cell lines with a tagged endogenous A3A, and will provide information on the nature of the interaction. Through these tests, my project aims to produce a greater understanding of how interacting proteins contribute to cancer mutagenesis through the regulation and dysregulation of A3A.

Body Composition Changes in Patients with Lung Cancer Prior to Diagnosis: Insights from the National Lung Screening Trial

Deena Snoke, PhD, Postdoc
Mentor: Michael Toth, PhD

Most patients with lung cancer have cancer cachexia (CC), a syndrome characterized by wasting of muscle and fat tissues, associated with poor treatment response and increased mortality. Little is known about early body composition (BC) changes in human CC prior to diagnosis, which may provide insight into mechanistic drivers of CC and identification of novel therapeutics. We conducted a secondary analysis of BC changes prior to diagnosis using AI-based analysis of computed tomography scans from the National Lung Screening Trial. Patients diagnosed with lung cancer with ≥ 2 scans before diagnosis (n=436) were paired with one participant who remained lung cancer-free after the same follow-up time as the cognate case (n=436). Using multivariate hierarchical modeling we estimated changes in adipose and muscle compartments in the years prior to patient diagnosis. Females diagnosed with advanced-stage cancer had reduced visceral adipose tissue (VAT) area indexed to height and increased VAT density approaching diagnosis compared with controls. In males, those with advanced-stage cancer showed decreased SAT density and loss of muscle prior to diagnosis compared with controls. Further studies are needed to evaluate other adipose depots and/or whole-body adiposity to fully characterize early BC changes during the development of lung cancer.

SciComms: Turning Findings into Headlines

Kate Strotmeyer, M.Ed.

Participants will learn best practices for research communications, including what's newsworthy, when and how to involve communications professionals, and tools and resources that are available through the University and cancer center.

Impact of Hospital-Acquired Venous Thromboembolism Subtypes on 10-day Mortality: Findings from the Medical Inpatient Thrombosis and Hemostasis Study

Aneta Strumilowska, Resident
Mentor: Karlyn Martin, MD

Background
While hospital-acquired venous thromboembolism (HA-VTE) has been associated with increased risk of in-hospital mortality, the associations of VTE subtypes – pulmonary embolism (PE), lower extremity deep vein thrombosis (LE DVT), and upper extremity DVT (UE DVT) - with mortality are less clear.

Methods
We included adults admitted for at least 1 midnight at 6 United States' hospital systems from 2016-2022 where VTE was not present at the time of admission. Each admission with HA-VTE was matched with up to 4 admissions without HA-VTE based on hospitalization day, age, sex, race, hospital system, level of care, and year. The hospital day of the HA-VTE, and the corresponding day for the admissions without HA-VTE, was defined as the index date. We categorized VTE into PE (± DVT), LE DVT (± UE DVT), and UE DVT only. The primary outcome was in-hospital mortality within 10 days of the index date. Adjusted conditional logistic regression estimated the associations of HA-VTE subtypes with mortality (Table).

Results
The matched cohort included 1,847 admissions with HA-VTE (610 PE, 686 LE DVT, and 551 UE DVT) and 7,077 admissions without HA-VTE. Mean age was 58 years, 43.7% were female, 54.6% were White race, and 24.4% were admitted to an ICU. Compared with admissions without HA-VTE, the adjusted odds ratios of mortality were 2.6 (95% confidence interval [CI] 1.4, 4.8) for PE, 2.1 (95% CI 1.2, 3.6) for LE DVT, and 0.73 (95% CI 0.34, 1.57) for UE DVT.

Conclusion
In a diverse patient cohort from six hospital systems, HA-PE and HA-LE DVT were associated with ~2-fold increased risk of mortality within 10 days, while HA-UE DVT was not associated with mortality. These data highlight heterogenous outcomes for various HA-VTE subtypes and have implications on the relative importance of outcomes for HA-VTE prevention studies.

A Volumetric Analysis of Timing and Duration of T2/FLAIR Changes on MRI Following Radiation Therapy in Patients with Low-Grade IDH-Mutant Glioma

Isabella Sutherland, Medical Student
Mentor: Alissa Thomas, MD

Background:
Patients with IDH-mutant low-grade glioma (LGG) can achieve many years of survival with radiation (RT) and chemotherapy. Distinguishing post-treatment MRI changes from true tumor progression is challenging and may lead to unnecessary interventions with harmful side effects. A better understanding of post-RT changes is essential for differentiating treatment effects from disease progression. This study characterizes volumetric changes in FLAIR hyperintensity following RT in LGG, to better understand the radiation-treatment effects or "pseudoprogression" that occurs in absence of true tumor regrowth.

Methods:
Serial MRIs of patients with LGG were reviewed pre-RT and up to 2.5 years post-RT. Segmentation for volumetric analysis was performed with manual supervision using ITK-SNAP (segmentation software). Descriptive statistics were reported.

Results:
Sixteen patients with grade 2 gliomas were included. 159 MRI scans were segmented using ITK-SNAP (median 9.5 MRIs/patient). Post-RT, 9/16 exhibited decreased FLAIR volumes, while 7/16 showed increases. Within the first year, 12/16 patients experienced subsequent FLAIR volume increases. FLAIR volumes stabilized or decreased a median of 18.4 months and mean of 15.0 months post-RT.

Conclusion:
FLAIR hyperintensity changes are highly variable in the first 1.5 years post-RT in LGG butr typically stabilize and decrease thereafter, likely indicating an inflection point for post-RT pseudoprogression stabilization.

Miro1-Mediated Mitochondrial Positioning in the Development and Metastasis of Breast Cancer

Randi Termos, PhD Candidate
Mentor: Brian Cunniff, PhD

Miro1 is a protein localized to the outer membrane of mitochondria that supports mitochondrial trafficking. Miro1 supports cell migration and proliferation of normal and tumor cells, including breast cancer. To investigate the role of Miro1 in breast cancer tumorigenesis and metastasis, we generated MDA-MB-231 human breast cancer cells with stable Miro1 knockdown (KD). Miro1 KD led to increased ERK1/2 phosphorylation and reduced proliferation, migration, and invasion. Xenografts of MDA-MB-231 Miro1 KD cells formed significantly smaller tumors compared to wild type MDA-MB-231 cells.
Next, we generated a novel transgenic mouse model that has inducible, tissue specific Miro1 deletion in mammary epithelial cells with concurrent polyomavirus middle T-antigen oncogene activation. We found that when cell transformation was induced Miro1 wild type mice formed tumors at all mammary gland sites, with metastasis to the lungs. Conversely, mice that had concurrent Miro1 deletion with middle T- antigen activation failed to develop tumors. Heterozygous mice with only one allele of intact Miro1 formed tumors with little ability to metastasize.
This data suggests that Miro1 has a functional role in both mammary tumor onset and tumor cell migration and invasion, providing a possible new biomarker of tumor status and pathway for therapeutic intervention.

Rurality and Screening Colonoscopy Participation in Patients with Lynch Syndrome

Isabel Thomas, Medical Student
Mentors: Kara Landry, MD; Tom Ahern, PhD; Peter Cataldo, MD

Authors: Isabel Thomas, Wendy McKinnon, George Davis, Laura Colello, Marc Greenblatt, Peter Cataldo, Thomas Ahern, Kara Landry

Background:
Screening colonoscopy reduces overall mortality for patients with Lynch Syndrome (LS). Several barriers to adherence are known but the impact of rurality is unclear.

Methods:
We enumerated a cohort of LS patients seen by the University of Vermont Cancer Genetics Program. We reviewed electronic medical records from 2021 to 2024. We defined screening compliance as undergoing ≥1 colonoscopy in a 3-year period. We classified rurality using Rural-Urban Commuting Area codes. We fit multivariable log-binomial and proportional odds regression models to estimate impacts of rurality and recency of genetics clinic visits on colonoscopy adherence.

Results:
We enrolled 201 LS patients. Compared with metropolitan/micropolitan, small town/rural residence was associated with a lower probability of having ≥1 colonoscopy (43% vs. 64%; RR=0.67, 95% CI: 0.49, 0.92), independent of age, sex, and PV. Recency of genetics clinic visit was associated with a higher probability of receiving ≥1 colonoscopy, independent of rurality.

Conclusions:
In a cohort of LS patients, small town/rural residence was associated with a lower probability of adherence to screening colonoscopy. Understanding and ameliorating this association should be prioritized. Our findings also support the importance of genetics longitudinal follow-up on colonoscopy adherence.

Risk Factors for Venous Thrombosis after Discharge from Medical Hospitalizations: The Medical Inpatient Thrombosis and Hemostasis (MITH) Study*

Ryan Thomas, MD

Authors: R. Thomas, A. Sparks, K. Wilkinson, M. Gergi, A. Repp, N. Roetker, N. Smith, P. Muthukrishnan, K. Martin, and N. Zakai

Background
Most studies of hospital-associated venous thromboembolism (VTE) either do not specifically assess post-discharge events or only assess risk factors at hospital admission rather than discharge.

Methods
Patients discharged from the University of Vermont Medical Center between January 2010 and September 2019 were followed for inpatient and outpatient VTE events for up to 90 days. Age-, sex-, race-, and length of stay-adjusted Cox models estimated the hazard ratios (HR) and 95% confidence intervals (CI) for potential risk factors for PD-VTE.

Results
Among 22,617 admissions, there were 180 PD-VTE events (90-day cumulative incidence of 0.8%). The median time from discharge to PD-VTE was 29 days. Prior history of VTE (3.34 HR; 2.26-4.93 95% CI) and active cancer (3.13 HR; 2.31-4.23 95% CI) were associated with increased risk of PD-VTE. Longer hospital stays (1.84 HR; 1.23-2.75 95% CI for 6-10 days and 1.64 HR; 0.93, 2.90 for 11+ days 95% CI), were associated with increased risk of post-discharge VTE. Both the mortality (1.22 HR 1.06-1.41 95% CI) and readmission (1.30 HR; 1.13-1.50 95% CI) Elixhauser Comorbidity Indices were associated with increased risk of PD-VTE.

Conclusions
Risk factors for VTE after discharge include characteristics related to hospitalization as well as patient specific risk factors and differ from those for VTE diagnosed during hospitalization. Age, length of hospital stay, discharge diagnoses, history of VTE, active cancer, and comorbidity indices increased the risk of PD-VTE. These data support that characteristics of the hospitalization influence PD-VTE risk and that risk assessment should be done at discharge.

Characterizing the Molecular Landscape of Sinonasal Squamous Cell Carcinoma

Jimmy Vareta, Post Doctoral Associate
Mentors: Princess Rodriguez, PhD; Julie Dragon, PhD; Scott Langevin, PhD, MHA, CT

Background:
Sinonasal squamous cell carcinoma (SNSCC) is a relatively rare malignancy, accounting for less than 3% of all head and neck cancers. Five-year overall survival for SNSCC ranges from 30 - 50% regardless of treatment. While recent whole-exome sequencing studies have shed light on the mutational landscape of numerous cancer types, no such systematic efforts have been reported for SNSCC, and therefore, common driver mutations for these malignancies remain largely unknown. The primary objective of this study was to address this gap in knowledge by comprehensively cataloging somatic mutations arising in SNSCC through next-generation whole-exome sequencing of a small cohort of tumor samples.

Patients and Methods:
This was a retrospective study in which next-generation whole-exome sequencing was performed on OCT-embedded tumor tissue and paired adjacent normal tissue from 12 patients diagnosed with incident SNSCC at the University of Cincinnati Cancer Institute from 2012–2014. Nf-core/sarek somatic variant calling workflow was used to detect and annotate somatic mutations and ECOLE deep learning model was used to detect somatic copy number alterations.

Results:
The average sequencing coverage in the cohort was 45x and 92.2% of reads achieved $\geq$ Q30, which is indicative of high-quality sequencing data. The median tumor mutation burden (TMB) in the cohort was 3.43 mutations per mega base consistent with TMB in the TCGA head and neck cancer cohort. No clear mutational pattern based on clinical and demographic variables was observed. We identified 263 genes that harbored two or more coding region mutations in multiple SNSCC tumors. Eight genes were significantly mutated ($q < 0.1$) with *TP53* being the most mutated gene with driver mutations in 6/12 (50%) of tumors. The 7 remaining significantly mutated genes (*NOTCH1*, *KMT2D*, *VWDE*, *FNBP4*, *SCAND3*, *NOD1* and *OR5C1*) displayed driver mutations in 17 - 33% of SNSCC tumors.

Conclusion:
This study helps elucidate the mutational landscape of SNSCC, advancing our understanding of common driver mutations and yielding potential new therapeutic avenues for management of this uncommon, though important, malignancy.

Mitotically-Associated Long Noncoding RNA (MANCR): A Novel Long Noncoding RNA that Promotes Genomic Stability and Cellular Proliferation in Triple Negative Breast Cancer

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Preventing end-stage Triple Negative Breast Cancer (TNBC) remains an unmet challenge. Long non-coding RNAs (lncRNAs) are epigenetic regulators functioning in the nucleus to support cellular stability and maintain the fidelity of chromatin interactions. We discovered that MANCR (LINC00704) is highly expressed in metastatic TNBC cells, supports cell survival *in vitro*, and MANCR expression correlates with poor patient survival. *In vitro* studies used short antisense nucleic acids (GapmerRs) to knockdown MANCR. For *in vivo* studies, TNBC cells were injected into the mammary fat pad of mice, tumors were established, and mice were treated with negative control or MANCR-targeting GapmeRs. MANCR genomic interactions were identified by chromatin isolation by RNA purification sequencing (ChIRP-seq). MANCR knockdown promotes DNA damage and decreases cell proliferation, migration, anchorage-independent colony formation, transwell invasion, and cellular survival. Targeting MANCR *in vivo* inhibits tumor growth and mass, TNBC cell circulation, and dissemination. MANCR ChIRP-seq revealed 1206 genome-wide binding sites: 48% intergenic, 52% genic. ChIRP peaks overlap with fragile sites, indicating MANCR provides genomic stability. These data suggest that targeting MANCR has therapeutic potential for patients with “MANCR-high” tumors by disrupting genome stability.

Breast Cancer Incidence and Surgical Trends Since the 2009 Changes to the US Preventive Services Task Force Screening Guidelines

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The 2009 USPSTF breast cancer (BC) screening guideline changes led to declines in screening mammography utilization, raising concern about potential increases in late-stage disease and more invasive surgical treatments. This study investigates BC stage at diagnosis and surgical treatment trends surrounding the 2009 changes.

Using 2004-2019 data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program in women ages 40+ years, we calculated age- and stage-specific BC incidence rates, proportions treated by partial vs. total vs. total mastectomy with reconstruction, and annual percent changes.

Rates of *in situ* BC decreased since 2009 (e.g. APC= -0.69 [95%CI:-2.77,-0.18], age 50-74). Localized BC rates increased steadily during 2004-2019 in ages 40-74 (e.g. APC=1.18 [95%CI:1.02,1.34], age 50-74). Regional and distant BC rates did not change or trends did not correlate with 2009. Partial mastectomy decreased during 2004-2012 (e.g. APC=-0.77 [95%CI:-2.96,-0.03]) while total mastectomy with reconstruction increased (e.g. APC=20.17 [95%CI:16.5,33.16]). During 2012-2019, total mastectomy decreased (e.g. APC=-2.44 [95%CI:-3.45,-1.61]), and partial mastectomy increased (e.g. APC=1.70 [95% CI:0.90,4.08]).

In situ BC decreased since 2009, consistent with declining screening mammography utilization since the guideline changes, but this decline did not appear to translate to more advanced BC stages at diagnosis or more invasive surgical treatment.