

**UC DAVIS
HEALTH**

**COMPREHENSIVE
CANCER CENTER**



32ND ANNUAL CANCER RESEARCH SYMPOSIUM

OCTOBER 29-30, 2026



FROM THE DIRECTOR

I am pleased to welcome you to the UC Davis Comprehensive Cancer Center's 32nd Annual Cancer Research Symposium. This year's theme, "Catalyst for a Cure: Connecting Innovation in Cancer Research", highlights the best cancer research efforts conducted by our Comprehensive Cancer Center members and brings together the many talents and passions of investigators devoted to solving the problem of cancer across the entire spectrum from prevention to survivorship.

The two-day in-person event is organized into five thematic sessions, designed to facilitate scientific interactions. It emphasizes collaboration across UC Davis while highlighting cutting-edge cancer research and the power of shared knowledge.

Internationally renowned clinician scientist Neeraj Agarwal, M.D. will deliver the David R. Gandara Lectureship on Developmental Therapeutics keynote address on "Personalizing Treatment of Metastatic Hormone-Sensitive Prostate Cancer".

Following the keynote presentation, the Clinical Research Session: A Focus on Pancreatic Cancer, chaired by Edward J. Kim, M.D., Ph.D., highlights state of the art insights on basic, translational, and clinical science disciplines focused on pancreatic cancer.

The Translational Research Session, chaired by Nicholas Mitsiades, M.D., Ph.D., focuses on how we are taking basic science research in glioma, leptomeningeal disease, metastatic disease, and biomarkers from bench-to-bedside.

The first day will conclude with a poster session and mixer in the lobby of Aggie Square. Hosted by the Cancer Center's Office of Education, Training, and Workforce Development, we invite you to join us for this exciting afternoon event highlighting cutting-edge cancer research from UC Davis while connecting with peers and colleagues across campus. Poster award winners will be announced at the conclusion of the symposium on Friday afternoon.

Friday's program will begin with the Global Oncology, Population Science, and Cancer Control Session, chaired by Shehnaz K. Hussain, Ph.D., Sc.M. This session will provide an overview of the UCDCCC Global Oncology Initiative and feature presentations examining the impact of cancer care across the United States, Philippines, and Latin America. Speakers will explore key global oncology challenges and opportunities, with additional focus on cancer survivorship, the unique needs of geriatric populations, and the epidemiological and population-level impacts of cancer. Together, these presentations will highlight disparities in cancer care and opportunities to advance equitable, evidence-based oncology care worldwide.

The Head and Neck Cancer Session, co-chaired by Stephanie Goldschmidt, D.V.M., and Xiao-Jing Wang, M.D., Ph.D., will serve as the concluding session of the symposium, showcasing state-of-the-art advances in discovery, therapeutics, prognosis, and early detection in head and neck cancer.

I am confident that this event will be an inspiring and highly productive experience for all who participate. Our team looks forward to engaging with you, exchanging ideas, and sharing new knowledge and discoveries throughout the symposium. We are deeply grateful for your continued support and extend our sincere appreciation to the symposium organizing committee for their dedication, time, and resources in making this event a success.

Sincerely,

Primo "Lucky" N. Lara, Jr., M.D., F.A.S.C.O.
Director, UC Davis Comprehensive Cancer Center
Distinguished Professor of Medicine
Executive Associate Dean for Cancer Programs
Codman-Radke Endowed Chair for Cancer Research

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Oncology

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AGENDA

THURSDAY, OCTOBER 29, 2026

7:30 - 8 a.m.	BREAKFAST
8 - 8:10 a.m.	Introduction and Welcome: Primo N. Lara, Jr., M.D., F.A.S.C.O. , Director, UC Davis Comprehensive Cancer Center
DAVID R. GANDARA LECTURESHIP ON DEVELOPMENTAL THERAPEUTICS	
8:10 - 8:15 a.m.	Primo N. Lara, Jr., M.D., F.A.S.C.O. <i>Dr. Gandara Lectureship Speaker Introduction and Award Presentation</i>
8:15 - 9 a.m.	Neeraj Agarwal, M.D., F.A.S.C.O. , Dana-Farber Cancer Institute, "Personalizing Treatment of Metastatic Hormone-Sensitive Prostate Cancer"
9 - 9:15 a.m.	Q&A
CLINICAL RESEARCH SESSION: A FOCUS ON PANCREATIC CANCER	
Chair: Edward J. Kim, M.D., Ph.D.	
9:15 - 9:25 a.m.	Introduction and Pancreatic Cancer State of the Art: Edward J. Kim, M.D., Ph.D.
9:25 - 9:40 a.m.	Edward J. Kim, M.D., Ph.D.; Yuanpei Li, Ph.D. "Clinical Translation of a Novel Autophagy Inhibitor for Pancreatic Cancer"
9:40 - 9:45 a.m.	Q&A
9:45 - 10 a.m.	Julie Sutcliffe, Ph.D. "Alphavbeta6 Integrin Targeted Radiotheranostics in patients with Metastatic Pancreas Cancer. Bench to Bedside"
10 - 10:05 a.m.	Q&A
10:05 - 10:20 a.m.	BREAK
10:20 - 10:35 a.m.	Ebaa Al-Obeidi, M.D. "Post-Adjuvant Residual Disease Evaluation by Circulating Tumor DNA for Pancreatic Cancer"
10:35 - 10:40 a.m.	Q&A
10:40 - 10:55 a.m.	Minh Duc Pham, Ph.D. Candidate "RUNX 1/2 - Mediated Chromatin Accessibility Governs the Activation of Cancer Associated Fibroblasts in Pancreatic Cancer"
10:55 - 11 a.m.	QandA
11 - 11:15 a.m.	Sean Judge, M.D. "Assessing Regional B7-H3 CAR T Cells for Pancreatic Cancer Liver Metastases"
11:15 - 11:20 a.m.	Q&A
TRANSLATIONAL RESEARCH SESSION	
Chair: Nicholas Mitsiades, M.D., Ph.D.	
11:20 - 11:25 a.m.	Introduction: Nicholas Mitsiades, M.D., Ph.D.
11:25 - 11:40 a.m.	Paul Knoepfler, Ph.D. "Targeting Epigenomic Machinery in H3.3 Mutant Pediatric Diffuse Midline Glioma"
11:40 - 11:45 a.m.	Q&A
11:45 - 12 p.m.	Maxine Umeh Garcia, Ph.D., M.S. "CSF-SEQ Reveals Prognostic Tumor and Host Transcriptional Programs in Leptomeningeal Disease"
12 - 12:05 p.m.	Q&A
12:05 - 1:10 p.m.	LUNCH
1:10 - 1:15 p.m.	Introduction: Nicholas Mitsiades, M.D., Ph.D.
1:15 - 1:30 p.m.	Randy Carney, Ph.D. "Analysis of Single Circulating Extracellular Vesicles as Liquid-Biopsy Biomarkers"
1:30 - 1:35 p.m.	Q&A
1:35 - 1:50 p.m.	Jack Goon, Ph.D. Candidate "Spatial Transcriptomic Impact of Immune-Radiotherapy on Systemic Anti-Tumor Immunity in Patients with Metastasis"
1:50 - 1:55 p.m.	Q&A
1:55 - 2:10 p.m.	Open Discussion and Invitation to Poster Session: Moderated by Nicholas Mitsiades, M.D., Ph.D.
POSTER SESSION AND MIXER - AGGIE SQUARE	
Hosted by: Cancer Center's Office of Education, Training, and Workforce Development	
2:25 - 3:25 p.m.	Poster Session: Part A
3:30 - 4:30 p.m.	Poster Session: Part B

FRIDAY, OCTOBER 30, 2026

7:30 - 8 a.m.

BREAKFAST

GLOBAL ONCOLOGY, POPULATION SCIENCE, AND CANCER CONTROL SESSION

Chair: Shehnaz K. Hussain, Ph.D., Sc.M.

8 - 8:05 a.m.

Introduction: Shehnaz K. Hussain, Ph.D., Sc.M.

8:05 - 8:20 a.m.

Elysia Alvarez, M.D., M.P.H.; Cameron Gaskill, M.D., M.P.H.

"Establishing a Global Oncology Initiative at the UC Davis Comprehensive Cancer Center"

8:20 - 8:25 a.m.

Q&A

8:25 - 8:40 a.m.

Victor K. Gozali, M.D., F.P.C.S., F.A.C.S., Makati Medical Center Cancer Institute, Philippines

"Perspectives on the Provision of Cancer Care in the Philippines"

8:40 - 8:45 a.m.

Q&A

8:45 - 9 a.m.

Joel Sanchez Mendez, Ph.D.

"Genome and Transcriptome-wide Association Studies of HER2-Positive Breast Cancer in Hispanic/Latina women in the United States and Latin America"

9 - 9:05 a.m.

Q&A

9:05 - 9:20 a.m.

Peter James, Sc.D., M.H.S.

"Residential Greenspace and Non-Small Cell Lung Cancer Survival in the California Cancer Registry 2017 – 2021"

9:20 - 9:25 a.m.

Q&A

9:25 - 9:40 a.m.

Alex Fauer, Ph.D., R.N., O.C.N.

"A Pilot Survivorship Navigation Trial using Practical Geriatric Assessments for Older Adult Cancer Survivors"

9:40 - 9:45 a.m.

Q&A

9:45 - 10 a.m.

Anjlee Mahajan, M.D.

"Clinical Epidemiology of Cancer Associated Thrombosis"

10 - 10:05 a.m.

Q&A

10:05 - 10:15 a.m.

BREAK

HEAD AND NECK CANCER SESSION

Chairs: Stephanie Goldschmidt, D.V.M. and Xiao-Jing Wang, M.D., Ph.D.

10:15 - 10:20 a.m.

Introduction: Stephanie Goldschmidt, D.V.M.

10:20 - 10:35 a.m.

Siao-Yi Wang, M.D., Ph.D.

"Advances in Head and Neck Cancer Discovery and Therapeutics: State of the Art"

10:35 - 10:40 a.m.

Q&A

10:40 - 10:55 a.m.

Stephanie Goldschmidt, D.V.M.

"Molecular Signatures of Squamous Cell Carcinoma with and without Locoregional Metastasis"

10:55 - 11 a.m.

Q&A

11 - 11:15 a.m.

Xiao-Jing Wang, M.D., Ph.D.

"Preclinical Studies and Clinical Trial for Targeting TGF- β , Time in Oligometastatic Head and Neck Cancer with SBRT and Immunotherapy"

11:15 - 11:20 a.m.

Q&A

11:20 - 11:35 a.m.

Andrew Birkeland, M.D.

"Leveraging Current Research to Inform the Next Generation of Immunotherapeutics for Head and Neck Cancer Clinical Trials"

11:35 - 11:40 a.m.

Q&A

11:40 - 11:55 a.m.

Open Discussion: Moderated by **Stephanie Goldschmidt, D.V.M.**

11:55 - 12:10 p.m.

Primo N. Lara, Jr., M.D., F.A.S.C.O.

"Celebration of the CCSG Renewal and Perspectives on the Next Five Years"

12:10 - 12:20 p.m.

Award Presentations and Final Remarks

Fred Meyers, M.D., M.A.C.P. and **Primo N. Lara, Jr., M.D., F.A.S.C.O.**

12:20 p.m.

Adjourn

SAVE THE DATE

33rd Annual Cancer Research Symposium: October 7 - 8, 2027

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DAVID R. GANDARA LECTURESHIP ON DEVELOPMENTAL THERAPEUTICS

“PERSONALIZING TREATMENT OF METASTATIC HORMONE-SENSITIVE PROSTATE CANCER”

Neeraj Agarwal, M.D., F.A.S.C.O.

Faculty Medical Oncologist, Dana-Farber Cancer Institute

Co-Director, Prostate Cancer Program, Harvard Cancer Consortium

The Lank Center for Genitourinary Oncology

Over the past decade, the treatment landscape for metastatic hormone-sensitive prostate cancer (mHSPC) — now called androgen pathway modulation-sensitive metastatic prostate cancer or APMS prostate cancer — has been transformed by the approval of multiple androgen receptor pathway inhibitors (ARPIs), which, combined with androgen deprivation therapy, have substantially extended

survival. As patients now live for many years, and in some cases a decade or longer, after diagnosis, the cumulative burden of treatment-related toxicity has become a central clinical concern. This talk will make the case that mHSPC care must now shift from a one-size-fits-all approach toward biomarker-guided personalization designed to maximize efficacy while minimizing unnecessary toxicity.

I will review PSA kinetics as a dynamic biomarker for escalating or de-escalating therapy and present data supporting SPOP mutation as a treatment-selection biomarker that predicts a favorable response to ARPI-based therapy but not to chemotherapy. In contrast, loss of PTEN, TP53, or RB1 identifies a poorer-prognosis, more aggressive phenotype that may warrant upfront treatment intensification with chemotherapy in addition to ARPI.

The talk will then turn to emerging predictive biomarkers that guide precision therapy selection: PSMA expression to identify candidates for lutetium-177-PSMA-617 radioligand therapy; homologous recombination repair gene mutations to identify candidates for PARP inhibitor combinations; and PTEN loss to identify candidates for AKT inhibitor (capivasertib)-based therapy.

Together, these data illustrate a paradigm shift in mHSPC or mAPMS Prostate cancer) management, from empiric, uniform treatment intensification toward genomically and biochemically informed, individualized therapy that optimizes long-term outcomes while preserving quality of life.

Dr. Neeraj Agarwal is a faculty Medical Oncologist at Dana-Farber Cancer Institute (DFCI), a teaching hospital of Harvard Medical School in Boston, Mass., United States. He is the Co-Director of the Prostate Cancer Program at the DFCI/Harvard Cancer Center. An internationally recognized leader in prostate cancer research, he has served as study chair or steering committee member for landmark trials leading to FDA and EMA approvals of apalutamide, olaparib, niraparib, and talazoparib for patients with advanced prostate cancer. Dr. Agarwal has authored over 590 publications, advanced novel therapies across prostate, kidney, and bladder cancers, and leads an NCI-funded R01 grant. A Fellow of the American Society of Clinical Oncology (ASCO), he has received multiple national awards for mentorship and scientific leadership, and currently serves as an executive officer for SWOG, an elected member of the ASCO Nominating Committee, and Chief Editor of *ASCO Daily News*.

ORAL PRESENTATION ABSTRACTS

THURSDAY

CLINICAL RESEARCH SESSION: A Focus on Pancreatic Cancer

Chair: Edward J. Kim, M.D., Ph.D.

CLINICAL TRANSLATION OF A NOVEL AUTOPHAGY INHIBITOR FOR PANCREATIC CANCER

Edward J. Kim, M.D., Ph.D., Professor, Department of Internal Medicine, and Yuanpei Li, Ph.D., Professor, Department of Biochemistry and Molecular Medicine

Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer-related death despite optimization of chemotherapy drug combinations that balance incremental extension of life with treatment-related toxicities. Recent development of RAS-targeted drugs justifiably warrant excitement but are still plagued by dose-limiting toxicities and ultimately resistance. Autophagy is a known mechanism of cancer cell survival and drug resistance in which scarce resources are recovered through engulfment of macromolecules and complete organelles into peri-nuclear double-membrane vesicles and degraded in lysosomes. Pancreatic cancer cells have relatively large lysosomes which are more fragile than normal-sized lysosomes. TR-002 is a novel autophagy inhibitor developed in Yuanpei Li's lab at UC Davis that self-assembles into nanoparticles and demonstrates highly potent antitumor activity in preclinical models. Extensive toxicology studies in rats and dogs demonstrated safety and provided dose range finding leading to an FDA IND approval for human clinical studies. Clinical grade drug was produced at the UCD GMP facility and scaled for clinical use. UCDCC 305 is a single-center, open-label, single-arm Phase 1 study of TR-002 in participants with advanced solid cancers in the dose escalation phase, followed by dose expansion phase in patients with refractory PDAC. The dose-escalation portion follows an accelerated dose escalation design until certain parameters dictate transition to standard 3+3 design. Eligible patients in the dose escalation cohort must have a solid tumor refractory to standard treatments whereas the dose expansion cohort will be limited to treatment-refractory advanced PDAC. The primary objectives are: 1) To determine the maximum tolerated dose (MTD), which will also be the recommended phase 2 dose (RP2D) of TR-002 for the treatment of advanced treatment-refractory solid tumors, and 2) To evaluate the toxicities of TR-002 administered intravenous weekly. Secondary objectives are: 1) To obtain preliminary assessment of anti-tumor activity of TR-002 administered intravenous weekly at the RP2D, and 2) To evaluate the pharmacokinetics of TR-002 administered intravenous weekly. The exploratory objectives is to assess the effects of TR-002 on pharmacodynamic biomarkers relating to the mechanism of action. To date, 7 patients have been consented and 3 patients enrolled with 2 treated on study.

ALPHAVBETA6 INTEGRIN TARGETED RADIOTHERANOSTICS IN PATIENTS WITH METASTATIC PANCREAS CANCER. BENCH TO BEDSIDE

Julie Sutcliffe, Ph.D., Professor, Department of Internal Medicine

Despite exhaustive testing and some encouraging advances in first-and second-line treatments, Pancreatic Ductal Adenocarcinoma (PDAC) remains the most lethal cancer. To address the clear unmet need for new therapies we proposed a novel molecularly targeted approach via the integrin subtype $\alpha\beta6$ using Peptide Receptor Radionuclide Therapy (PRRT). The $\alpha\beta6$ integrin is an epithelial-specific cell surface receptor that is undetectable in healthy adult epithelium but is significantly up-regulated in a wide range of cancers including pancreatic. We have developed the [68Ga]Ga DOTA-5G / [177Lu]Lu DOTA-ABM-5G theranostic pair. [68Ga]Ga DOTA-5G is an $\alpha\beta6$ -integrin-targeted peptide that is radiolabeled with Gallium-68 (half-life 68 minutes) and is being developed as a diagnostic. [177Lu]Lu DOTA-ABM-5G contains the same $\alpha\beta6$ -integrin-targeted peptide but is appended with an albumin binding moiety (ABM) to extend the circulation half-life, and is radiolabeled with Lutetium-177 (half-life 6.643 days), and is being developed as a radiotherapy.

In this Phase I, first-in-human study we are evaluating the safety and efficacy of a [68Ga]Ga DOTA-5G / [177Lu]Lu DOTA-ABM-5G theranostic pair in patients with locally advanced or metastatic PDAC (NCT04665947). [68Ga]Ga DOTA-5G PET imaging is being used diagnostically to select patients that have $\alpha\beta6$ -avid disease who are then eligible for treatment with the [177Lu]Lu DOTA-ABM-5G. The ability to visualize the disease with [68Ga]Ga DOTA-5G is a patient centered approach for [177Lu]Lu DOTA-ABM-5G treatment and has the potential to radically alter the treatment of PDAC through increased efficacy and reduced toxicity.

To date we have imaged 40 patients using [68Ga]Ga DOTA-5G PET/CT imaging and treated 26 patients with [177Lu]Lu DOTA-ABM-5G. Both agents were well tolerated and no treatment related SAEs observed. We have demonstrated that [68Ga]Ga DOTA-5G PET can be used to visualize disease and select patients for [177Lu]Lu DOTA-ABM-5G treatment. Using [68Ga]Ga DOTA-5G PET we have detected lesion in lung, liver, bone and brain and in some cases identified lesions that were not previously identified using standard-of-care imaging. We have demonstrated that the [177Lu]Lu DOTA-ABM-5G treatment reaches the target and efficacy is suggested at the highest dose level (single cycle) and will be determined during an additional dose finding study (multi-cycle).

POST-ADJUVANT RESIDUAL DISEASE EVALUATION BY CIRCULATING TUMOR DNA FOR PANCREATIC CANCER

Ebaa Al-Obeidi, M.D., Assistant Professor, Department of Internal Medicine

Background: Despite curative-intent resection and adjuvant chemotherapy, recurrence rates remain high in pancreatic cancer. Circulating tumor DNA (ctDNA) has emerged as a sensitive marker of minimal residual disease (MRD), but its utility as a predictive biomarker to guide therapeutic intervention remains unclear.

Methods: Our investigator initiated clinical trial titled PREDICTS Panc (Post-adjuvant Residual disease Evaluation by circulating tumor DNA

for Initiation of ChemoTherapy Salvage for Pancreatic cancer) is a phase II pragmatic, single-arm interventional study evaluating the clinical utility of ctDNA-guided salvage therapy in patients with resected pancreatic cancer. Eligible patients must have completed surgery and adjuvant chemotherapy, demonstrate ctDNA positivity by the tissue-informed Signatera™ Genome (Natera™) assay, and have no recent radiographic evidence of disease recurrence. Participants will initiate a prespecified salvage systemic therapy regimen, selected according to prior treatment exposure, within four weeks of a positive ctDNA result. Patients will receive at least three months of protocol-directed salvage therapy, with continuation thereafter at the treating physician's discretion.

Endpoints: The primary endpoint is the 3-month radiographic recurrence-free survival (RFS) rate, compared with historical controls. Secondary endpoint is 6-month radiographic RFS rate and exploratory endpoints are time to ctDNA clearance as well as serial ctDNA levels at each radiographic assessment.

Hypothesis: Salvage systemic therapy in patients with ctDNA-detected MRD but no radiographic evidence of disease will delay disease recurrence and improve short-term radiographic recurrence-free survival.

RUNX1/2-MEDIATED CHROMATIN ACCESSIBILITY GOVERNS THE ACTIVATION OF CANCER ASSOCIATED FIBROBLASTS IN PANCREATIC CANCER

Minh Duc Pham, Ph.D. Candidate, Department of Microbiology and Molecular Genetics

Pancreatic ductal adenocarcinoma (PDAC) remains the deadliest cancer with only 13% of five-year survival rate in patients. However, effective drug delivery and administration of immunotherapy have been limited due to the dense fibrotic stroma in PDAC tumor microenvironment, majorly contributed by cancer-associated fibroblasts (CAFs). Unfortunately, targeting CAFs has not yet been successful due to the lack of understanding in CAF activation, heterogeneity, and plasticity. Of note, CAFs do not genetically differ from their origins, and they are interconvertible depending on external factors and signaling cues. This plasticity feature suggests that CAFs activation is regulated by epigenetic reprogramming. Using ATAC-seq and innovative PDAC organoid-CAF co-culture models, we revealed distinct chromatin accessibility profiles of two major CAF subtypes, myofibroblasts (myCAF) and inflammatory fibroblasts (iCAFs) in vitro. In parallel, snATAC-seq analysis on both patient samples and mouse models also indicated the role of chromatin accessibility in differentiating CAF subtypes. Interestingly, we discovered a universal inflammatory-to-myofibroblastic process, in which fibroblasts were initially activated into iCAFs and gradually transitioned into late-stage LRR15+ myCAFs. Notably, this activation towards myofibroblasts is tightly regulated by RUNX1/2 transcription factors. Both pharmacological inhibition and genetic perturbation targeting RUNX1/2 significantly repressed CAF activation into either myCAFs or iCAFs and suppressed tumor organoid-fibroblast crosstalk in co-culture settings. Additionally, knocking out of Runx1/2 in fibroblasts markedly reduced collagen deposition and tumor growth in orthotopic co-transplantation mouse models. Overall, our study demonstrates the epigenetic basis of CAF plasticity and suggests a therapeutic strategy targeting the RUNX1/2 family to remodel the stroma and improve treatment outcomes.

ASSESSING REGIONAL B7-H3 CAR T CELLS FOR PANCREATIC CANCER LIVER METASTASES

Sean Judge, M.D., Assistant Professor, Department of Surgery

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease with frequent metastasis to the liver. Novel liver-directed therapies are needed to improve outcomes for PDAC patients. CAR T therapy has shown great clinical success in hematological malignancies but has shown limited efficacy for solid tumors, including PDAC. Challenges include limited trafficking and engraftment of CAR therapy into the tumor. The goal of this study was to investigate regional delivery of B7-H3 CAR T therapy via portal vein to improve the trafficking and engraftment of CAR T cells to treat PDAC liver metastases.

Methods: Xenogeneic PDAC liver metastases were generated by injecting 10^6 luciferase-tagged PANC-1 cells into NSG mice via hemi-spleen method. After 14 days, B7-H3 CAR T or untransduced (UnT) T cells (10^7 cells/kg dose) were injected into the portal vein and survival and tumor burden were assessed. Liver met-bearing mice were treated 14 days after tumor implantation with 10^6 B7-H3 CAR T cells administered via portal vein or tail vein and assessed for CAR T engraftment and phenotype five days post-administration.

Results: B7-H3 CAR T cells administered via portal vein demonstrate complete elimination of PANC-1 liver metastases within four weeks and increased survival compared to UnT. B7-H3 CAR T cells administered via portal vein showed increased liver engraftment five days after administration compared to IV administration. CD8 CAR T cells administered via portal vein also demonstrated higher expression of liver tissue residency markers including CD49a, CXCR6, and CD103.

Conclusions: Portal vein administration of B7-H3 CAR T cells treats xenogeneic PDAC liver metastases within four weeks and demonstrates superior engraftment and liver residency markers five days after administration compared to systemic administration. These findings demonstrate efficacy of portal vein delivery of B7-H3 CAR T therapy to treat PDAC liver metastases and support early phase clinical studies of portal venous cellular therapy.

TRANSLATIONAL RESEARCH SESSION

Chair: Nicholas Mitsiades, M.D., Ph.D.

TARGETING EPIGENOMIC MACHINERY IN H3.3 MUTANT PEDIATRIC DIFFUSE MIDLINE GLIOMA

Paul Knoepfler, Ph.D., Professor, Department of Cell Biology and Human Anatomy

Pediatric diffuse midline glioma (DMG) with histone H3.3 mutations such as K27M are fatal tumors exhibiting an array of epigenetic changes. DMG are thought to arise from oligodendrocyte precursor cell (OPC)-like cells that have both altered epigenetic states and misexpression of key neurodevelopmental pathways that contribute to tumorigenesis. A central challenge has been to identify targetable elements of such epigenetic oncogenic pathways in DMG. In the present study we have identified specific epigenomic machinery downstream of K27M in DMG, elements of which appear to be dependencies of these tumors. One type of DMG dependency is neurodevelopmental basic-helix-loop-helix transcription factors including MYC family and ASCL1 factors. These K27M-induced transcription factors also recruit chromatin-modifying enzymes that are targetable with specific inhibitors, representing another kind of potential therapeutic target. Finally, we have also identified a K27M-related miRNA pathway in DMG that is targetable and miRNAs themselves may have therapeutic activities. Overall, these mutant H3.3-related elements may also function as a coordinate oncogenic network in DMG. Our work suggests this network is important for altering chromatin states, including increasing chromatin accessibility, in DMG responsible for oncogenic gene expression. These studies provide hope for future therapeutic approaches for DMG.

CSF-SEQ REVEALS PROGNOSTIC TUMOR AND HOST TRANSCRIPTIONAL PROGRAMS IN LEPTOMENINGEAL DISEASE

Maxine Umeh Garcia, Ph.D., M.S., Assistant Professor, Department of Internal Medicine

Background: Leptomeningeal disease (LMD) is a devastating complication of advanced cancer associated with rapid neurologic decline and poor survival. Current diagnostic approaches rely on cerebrospinal fluid (CSF) cytology and neuroimaging, both of which have limited sensitivity and provide little insight into disease biology. We developed CSF-Seq, a whole-transcriptome sequencing approach for cell-free RNA (cfRNA) from CSF, to characterize molecular programs associated with LMD and identify clinically relevant biomarkers.

Methods: We analyzed 125 prospectively collected CSF samples spanning multiple disease states, including breast and lung LMD, glioblastoma, traumatic brain injury, and non-cancer neurologic controls. Through optimized cfRNA extraction, library preparation, and deep sequencing, we performed transcriptome-wide analyses to identify disease-associated gene expression patterns, biologic pathways, and prognostic signatures.

Results: CSF-Seq generated reproducible transcriptome-wide profiles despite the low abundance and fragmented nature of CSF cfRNA. LMD samples exhibited distinct transcriptional programs that separated them from non-cancer controls and non-LMD cancers. Tumor-associated epithelial transcripts, including CEACAM6, MUC1, EPCAM, KRT7, and KRT19, were consistently enriched in LMD. Pathway and network analyses revealed coordinated epithelial and proliferative programs, including cell-cycle regulation, chromosome segregation, E2F targets, G2/M checkpoint regulation, and MYC-associated transcriptional pathways, alongside altered representation of CNS-associated transcriptional programs. Importantly, we identified a CSF collection method-independent LMD transcriptional signature that captured these coordinated disease-associated programs. High signature expression was significantly associated with shorter overall survival and remained associated with increased hazard of death after adjustment for relevant covariates.

Conclusions: CSF-Seq enables minimally invasive transcriptome-wide characterization of LMD and reveals biologically coherent disease-associated programs linked to patient outcomes. These findings establish CSF cfRNA as a complementary molecular source of information beyond conventional cytology and imaging and provides a framework for biological discovery, patient stratification, and longitudinal monitoring in LMD and other CNS pathologies.

ANALYSIS OF SINGLE CIRCULATING EXTRACELLULAR VESICLES AS LIQUID-BIOPSY BIOMARKERS

Randy Carney, Ph.D., Associate Professor, Department of Biomedical Engineering

Background: Immune checkpoint inhibitors have transformed oncology, yet only a minority of patients achieve durable clinical benefit, and tissue PD-L1 remains a static, imperfect predictor of response. Circulating extracellular vesicles (EVs) carry tumor- and immune-derived proteins and surface glycans, offering a minimally invasive, repeatable liquid-biopsy window into the tumor-immune interface. We are developing a single-EV platform to characterize EV immune-checkpoint proteins, Raman spectral fingerprints, and glycosylation as predictive and dynamic biomarkers of immunotherapy response, designed to generalize across solid tumors.

Methods: Plasma EVs were isolated using size-exclusion approaches, with additional affinity based orthogonal capture (TIM4 phosphatidylserine vs. CD9/CD63/CD81 tetraspanins) to assess method bias. Single-EV super-resolution imaging by single-molecule localization microscopy quantified per-vesicle positivity and co-positivity for pan-tetraspanin EV markers and immune checkpoints (e.g., PD-L1, PD-1, CD80). Broad label-free Raman spectral imaging was performed on EVs concentrated into evaporative “coffee ring” deposits by Marangoni flow, with spatially resolved spectra across the ring classified by machine learning. In parallel, lectin-based assays began profiling cancer-relevant surface glycans. Explainable models (regularized regression with SHAP feature attribution) derived interpretable signatures that were applied across head and neck (HNSCC) and thoracic (NSCLC) cohorts.

Results: Across dozens of patient plasma samples analyzed to date, the platform resolves single-EV immune-checkpoint protein signatures at sub-vesicle resolution. Initial results are encouraging: EV checkpoint profiles and Raman spectral imaging are measurable in patient plasma and provide contrast to separate patients by disease classification and treatment response, and feature attributions remain clinically interpretable. Surface-glycan measurements are also coming online, and early data suggest they contribute an orthogonal glyco-immune dimension. Assay reproducibility comparisons support a scalable, clinic-compatible workflow.

Conclusions: Integrated single-EV profiling may provide a generalizable, interpretable, and minimally invasive approach to predict and monitor immunotherapy response. These initial findings establish feasibility and motivate prospective, multi-cohort validation toward EV-guided clinical decision support.

SPATIAL TRANSCRIPTOMIC IMPACT OF IMMUNE-RADIOTHERAPY ON SYSTEMIC ANTI-TUMOR IMMUNITY IN PATIENTS WITH METASTASIS

Jack Goon, Ph.D. Candidate, Department of Pathology and Laboratory Medicine

Immune checkpoint inhibitors (ICIs) are the standard of care for many solid tumors, though only a subset of patients respond. Stereotactic body radiotherapy (SBRT) modulates local and systemic immunity and therefore may synergize with ICI to treat metastatic disease. However, the impact and underlying mechanisms of immune-radiotherapy on systemic anti-tumor immunity are not fully understood.

In this prospective pilot study, we evaluate the combination of Atezolizumab (an anti-PD-L1 monoclonal antibody) and SBRT in patients with metastatic solid tumors. This single-institution phase I trial (NCT02400814) enrolled patients with ≥ 2 measurable lesions, including one amenable to SBRT. Patients received Atezolizumab (1200 mg IV every 3 weeks) combined with SBRT (50 Gy in 5 fractions to one lesion), delivered either concurrently or following 3 cycles of induction Atezolizumab. Changes in systemic immunity were assessed by spatial transcriptomic profiling of pre-treatment (n=7) and non-targeted post-treatment (n=7; 5 paired) tumor biopsies. Cells were grouped into tumor, stroma, interface, and immune-niche neighborhoods based on spatial proximity. Differential abundance, gene expression, and gene set enrichment analyses were conducted. Bulk RNA sequencing analysis was also conducted on PBMCs pre- and post-treatment.

Spatial transcriptomics detailed changes in the tumor immune microenvironment of non-target lesions. The composition of the tumor microenvironment, in terms of cell type or neighborhood, did not change significantly with treatment. Interestingly, the quantity of immune-niche neighborhood post-treatment strongly correlated with overall survival ($p < 0.0001$), and a gene score derived from immune-niche cells correlated with overall survival in independent datasets. Cells within the immune-niche observed changes in gene expression post-treatment, including a decrease in interferon response gene expression. In bulk RNA sequencing of PBMCs, treatment induced differential expression of gene sets related to proliferation, immune activation, and DNA damage repair.

In total, these findings indicate that immune-radiotherapy with SBRT targeting one lesion has systemic impacts on immunity that may not have occurred with ICI alone, including on circulating cells and non-target lesions at the spatial, gene expression level. Further, we identify the immune-niche neighborhood as a prognostic factor for immune-radiotherapy of solid tumors, which will inform biomarker design and drug development.

ORAL PRESENTATION ABSTRACTS

FRIDAY

GLOBAL ONCOLOGY, POPULATION SCIENCE, AND CANCER CONTROL

Chair: Shehnaz K. Hussain, Ph.D., Sc.M.

ESTABLISHING A GLOBAL ONCOLOGY INITIATIVE AT THE UC DAVIS COMPREHENSIVE CANCER CENTER

Elysia Alvarez, M.D., M.P.H., Associate Professor, Department of Pediatrics, and Cameron Gaskill, M.D., M.P.H., Associate Professor, Department of Surgery

Cancer is a leading cause of morbidity and mortality worldwide, yet disparities in prevention, diagnosis, and treatment persist across both international and local settings. The UC Davis Comprehensive Cancer Center (UCDCCC), an NCI-designated Comprehensive Cancer Center serving a uniquely diverse 19-county catchment area in Northern California and the Central Valley, is launching a Global Oncology Initiative to address this burden through bidirectional partnership.

Grounded in UC Davis's mission to improve quality of life for all and aligned with the UC Davis Center for Global Health's philosophy that global engagement strengthens scientific rigor. The Initiative operates on a central premise: progress in local and global cancer care are mutually reinforcing. UCDCCC's catchment area is home to immigrant, rural, agricultural, and other underserved populations, offering cancer epidemiology and care-delivery challenges that mirror those faced by international partners, positioning UCDCCC to translate insight in both directions.

The Initiative's core components include collaborative translational research responsive to shared and region-specific cancer burdens; reciprocal clinical and educational exchange with international partner institutions; and structured training pathways for oncology clinicians, scientists, and public health leaders across career stages. Guiding values of equity, reciprocity, scientific rigor, community trust, and next-generation leadership, inform the next steps in the Global Oncology Initiative.

This presentation outlines the Initiative's founding framework, initial partnership sites, and early research priorities, and invites discussion on models for sustainable, equity-centered global oncology collaboration between academic cancer centers and global partners.

PERSPECTIVES ON THE PROVISION OF CANCER CARE IN THE PHILIPPINES

Victor K. Gozali, M.D., F.P.C.S., F.A.C.S., Makati Medical Center Cancer Institute, Philippines

Cancer care in the Philippines is guided by the National Integrated Cancer Control Act (NICCA)– Republic Act No. 11215, which aims to make cancer treatment more accessible, affordable and comprehensive across the continuum of care. The Law signed in February 2019 mandates expanded Philhealth (National Insurance) benefit packages, the creation of Regional and Specialty Cancer Centers, the establishment of a National Cancer Registry and the Philippine Cancer Center. Significant developments provided by the Philippine government through the Department of Health has moved the effort of "Universal Health Coverage for every Filipino" achievable. In line with this NICCA Law, Makati Medical Center Cancer Center applied for accreditation with the Department of Health and was approved and certified as the first Cancer Specialty Center in the Hospital category. Furthermore, MMC Cancer Center signed a Memorandum of Understanding (MOU) for cooperation with UC Davis Comprehensive Cancer Center (UCDCCC) in April 2019 which is still in effect at present. It includes second opinion consultations for difficult cases with the team of experts from UCDCCC, as well as 3 Postgraduate courses in the past with exclusive speakers from UCDCCC.

GENOME AND TRANSCRIPTOME-WIDE ASSOCIATION STUDIES OF HER2-POSITIVE BREAST CANCER IN HISPANIC/LATINA WOMEN IN THE UNITED STATES AND LATIN AMERICA

Joel Sanchez Mendez, Ph.D., Postdoctoral Scholar, Department of Public Health Sciences

Breast cancer is the most common cancer among women worldwide. Genome Wide Association Studies (GWAS) have identified genetic variants associated with overall and estrogen receptor-specific breast cancer risk. However, genetic drivers of HER2-positive disease remain poorly understood, particularly among Hispanic/Latina (H/L) women, who are more likely than non-Hispanic White women to be diagnosed with this subtype. Thus, we conducted the first GWAS and fine-mapping of HER2-positive breast cancer in H/L women to identify subtype-specific genetic variants.

We leveraged data from eight studies comprising participants from seven countries in Latin America and the United States to conduct multi-ancestry GWAS. Individual-level genotyping data (4,857 cases and 8,867 controls) were processed through a harmonized quality-control pipeline and imputed to TopMed (r2@1.0.0). We performed GWAS within each study controlling for the first ten principal components and age in PLINK v1.9. Results were meta-analyzed using a fixed-effect model in METAL (9,381,563 variants analyzed). Candidate single nucleotide polymorphisms (SNPs) were evaluated for heterogeneity between HER2-positive vs. HER2-negative disease. SNPs with HER2-positive-specific associations were carried forward for expression quantitative trait locus (eQTL), colocalization, and Transcriptome-Wide Association (TWAS) analyses to identify candidate genes.

We identified 133 genome-wide significant ($p \leq 5e-8$) and 298 suggestive SNPs ($p \leq 1e-7$) associated with HER2-positive disease. Of these, 251 preferentially associated with HER2-positive disease (p -heterogeneity < 0.05). Clumping analyses highlighted five HER2-positive regions. Two lead SNPs (rs140068132 and rs41289379) mapped to 6q25 region, previously associated with breast cancer risk in H/L women. One lead variant mapped to the 8q21 region, while another tagged the 21q22.3 locus. We also identified a novel variant, rs12484512 at 22q12.3, not previously associated with overall or subtype-specific breast cancer risk. Carriers of the minor allele had 46%

higher risk of HER2-positive breast cancer (OR =1.46; $p = 3.7\text{e-}7$). EQTL and colocalization suggested that rs12484512 regulates expression of the solute carrier family 5 member 4 (SLC5A4) gene. TWAS demonstrated an association between SLC5A4 and HER2-positive disease ($p = 1.1\text{e-}4$) but not HER2-negative disease ($p=0.17$).

We present the first GWAS and fine-mapping study of HER2-positive breast cancer in H/L women. Our findings identify three subtype-specific variants, including the novel rs12484512, which implicates SLC5A4 as a potential contributor to HER2-positive disease.

RESIDENTIAL GREENSPACE AND NON-SMALL CELL LUNG CANCER SURVIVAL IN THE CALIFORNIA CANCER REGISTRY 2017-2021

Peter James, Sc.D., M.H.S., Professor, Department of Public Health Sciences

Objective: To examine the prospective association between residential greenness exposure and non-small cell lung cancer (NSCLC) survival in California.

Material and Methods: All patients diagnosed with NSCLC in California between 2017 and 2021 were identified in the California Cancer Registry. We used time-varying Landsat Normalized Difference Vegetation Index (NDVI) for April in a 270m buffer around participants' geocoded residential addresses as our greenspace exposure. We examined the association between NDVI and all-cause survival and cancer-specific survival using Cox proportional hazards models adjusted for age, sex, race/ethnicity, cancer stage, and tobacco use with follow-up through July 2023. Models were stratified by neighborhood level socioeconomic status (SES).

Results: Among 49,209 NSCLC patients (mean age 71 at baseline, mean follow-up 2.2 years), 50.4% were female, 61.5% were non-Hispanic white, and 25.3% were never-smokers. Higher NDVI was associated with better all-cause survival (hazard ratio [HR] 0.97 [95% CI 0.96, 0.98] and cancer-specific survival (HR 0.97 [95% CI 0.96, 0.98]) per 0.1 higher NDVI. In stratified models, the positive association between NDVI and all cause survival was only observed among patients residing in the highest tertile of SES (HR=0.97 [0.95, 0.99] per 0.1 higher NDVI), whereas higher NDVI was not associated with all cause survival for patients residing the highest in the lowest tertile of SES (HR=1.01 [0.99-1.02] per 0.1 higher NDVI) (p for interaction: 0.043). Stratified results were consistent for cancer-specific survival.

Conclusion: We observed that higher greenness exposure was associated with improved all-cause and cancer-specific survival among California patients with a newly diagnosed NSCLC. We observed qualitative effect modification by neighborhood SES, where greenspace was protective only in high SES neighborhoods. This suggests that greenspace quality or accessibility may differ in high versus low SES neighborhoods, with implications for cancer survival.

A PILOT SURVIVORSHIP NAVIGATION TRIAL USING PRACTICAL GERIATRIC ASSESSMENTS FOR OLDER ADULT CANCER SURVIVORS

Alex Fauer, Ph.D., R.N., O.C.N., Assistant Professor, Betty Irene Moore School of Nursing School

Background: We conducted and evaluated the feasibility and preliminary efficacy of a practical geriatric assessment and paired tailored survivorship navigation intervention.

Methods: Eligible patients were cancer survivors aged 65-90 years diagnosed with stage II to III breast, colorectal, or prostate cancer at a comprehensive cancer center. A community health worker trained in geriatric assessment, social support, and local aging resources conducted a 4 month intervention over 3 visits: practical geriatric assessment at month 0 and survivorship navigation at 2 and 4 months. The primary endpoint was feasibility, pre-specified as >65% retention, defined as completion of intervention visits and a 6 month assessment. Secondary endpoints were patient-reported outcomes (PROMIS anxiety, depression, physical function, self-efficacy, emotional support), and quality of life at 6 months compared with baseline (trial entry). Endpoints were summarized with descriptive statistics, bivariate tests, and effect sizes. The trial was registered on ClinicalTrials.gov (NCT#06125145).

Findings and Interpretation: We enrolled 28 participants (mean age 72.4, range 67-83) from April 2024 to June 2025 at a single comprehensive cancer center. Among these participants, 23 (82%, one-sided 90% CI=66%) completed the 6 month follow-up, which met our definition of feasibility (one-sided $p=0.037$). At 6 months vs. baseline, anxiety decreased by a minimally clinically important difference in 43% (N=10/23, effect size 0.36, 95%CI -0.2, 0.92), and most participants self-reported greater self-efficacy (52%, N=12/23), and no change in depression (43%, N=9/23).

Discussion: A practical geriatric assessment with tailored navigation intervention is feasible in survivorship. Future steps include testing with a fully powered, confirmatory trial.

CLINICAL EPIDEMIOLOGY OF CANCER ASSOCIATED THROMBOSIS

Anjee Mahajan, M.D., Assistant Professor, Department of Internal Medicine

Cancer-associated thrombosis (CAT) is an important cause of morbidity and mortality for patients with malignancy and varies by primary cancer type, stage, and therapy. We aimed to characterize the incidence, risk factors, temporal trends, and the effect on mortality of CAT. The California Cancer Registry was linked to the statewide hospitalization database to identify individuals with the 13 most common malignancies diagnosed between 2005 and 2017 and determine the 6- and 12-month cumulative incidence of CAT by venous thromboembolism (VTE) location, tumor type, and stage after adjusting for competing risk of death. Cox proportional hazard regression models were used to determine risk factors associated with CAT and the effect of CAT on all-cause mortality. 942 019 patients with cancer were identified; 62 003 (6.6%) had an incident diagnosis of CAT. Patients with pancreatic, brain, ovarian, and lung cancer had the highest, and patients with breast and prostate cancer had the lowest 12-month cumulative incidence of CAT. For most malignancies, men, those with metastatic disease and more comorbidities, and African Americans (vs non-Hispanic Whites) were at highest risk for CAT. Patients diagnosed with cancer between 2014 and 2017 had a higher risk of CAT compared with those diagnosed between 2005 and 2007. CAT was associated with increased overall mortality for all malignancies (HR ranges 1.89 to 4.79). The incidence of CAT increased over time and was driven by an increase in pulmonary embolism±deep vein thrombosis (PE±DVT). CAT incidence varies based on tumor type and stage and on individual risk factors including gender, race/ethnicity, and comorbidities. For all tumor types, CAT is associated with an increased mortality.

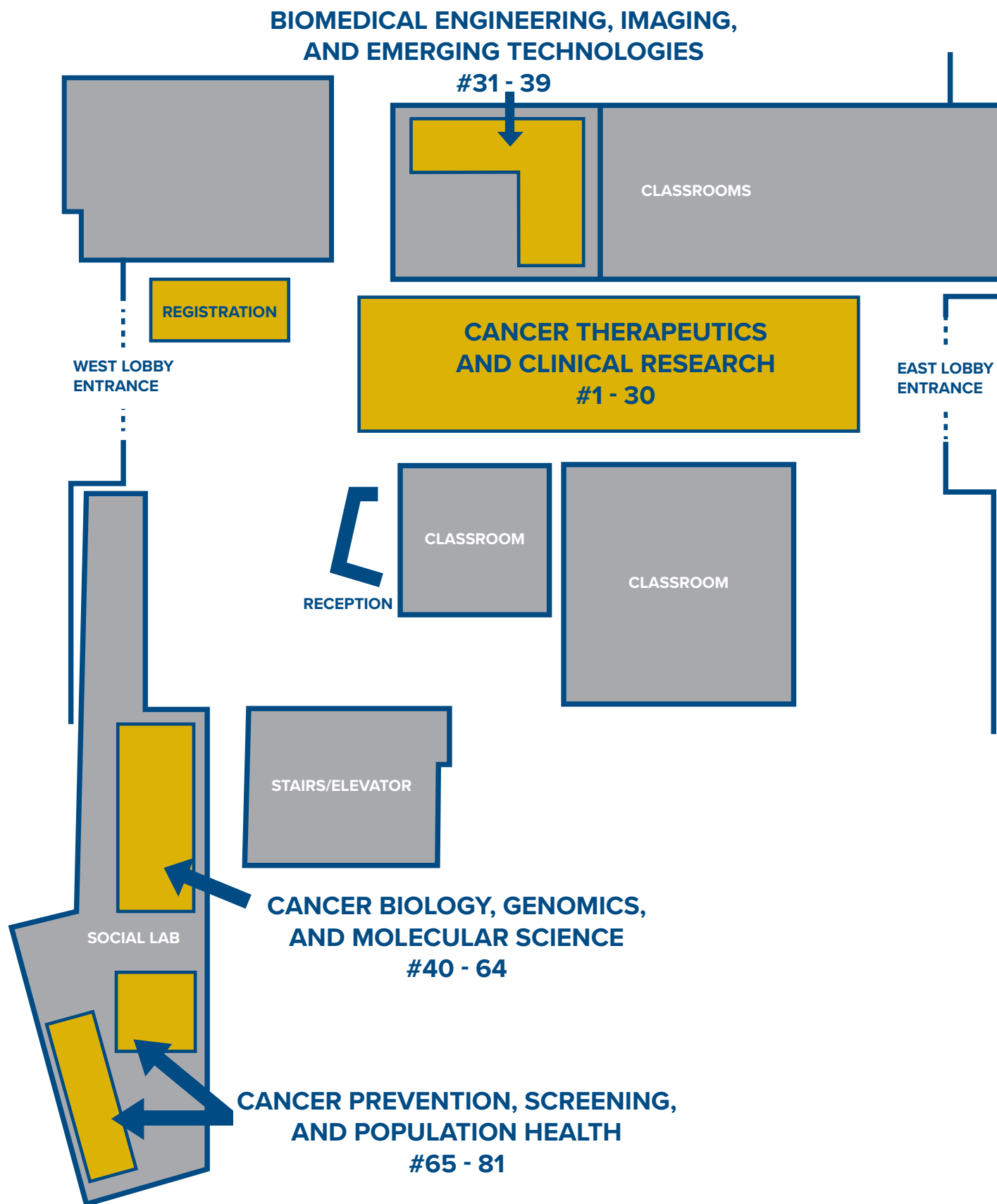
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POSTER SESSION MAP



POSTER PRESENTATION ABSTRACTS

NEIGHBORHOOD: CANCER THERAPEUTICS AND CLINICAL RESEARCH

1-A REDOX-RESPONSIVE POLYMER NANOPARTICLES FOR GD2-TARGETED BIORNA DELIVERY IN HIGH-RISK NEUROBLASTOMA

Yu-Rim Ahn, Postdoctoral Scholar^{1,3}, Aming Yu^{2,3}, Jinhwan Kim^{1,3}, Erin G. Brown^{1,3}

¹Department of Surgery, UC Davis, Sacramento, CA; ²Department of Biochemistry and Molecular Medicine, UC Davis, Sacramento, CA; ³UC Davis Comprehensive Cancer Center, Sacramento, CA

Introduction: High-risk neuroblastoma (HRNB) is a pediatric solid tumor that requires advanced therapeutic strategies. While microRNAs (miRs), including miR-124, can regulate multiple oncogenic pathways, their clinical application is limited by systemic instability and poor tumor specificity. To address these challenges, we developed a stimuli-responsive, bioreducible polymer nanoparticle (PNP) platform tailored for targeted and efficient bioengineered miR delivery to HRNB.

Method: Low molecular weight (LMW) polyethylene imine (PEI) (1.2 kDa) was thiolated and cross-linked via disulfide bonds to impart redox-responsiveness. The resulting polymer was modified with polyethylene glycol (PEG) (2 kDa) and 3-aminophenylboronic acid (PBA) to target GD2 gangliosides, followed by complexation with bioengineered miR-124 (PBA-PNP). PBA-PNPs were characterized using dynamic light scattering (DLS), zeta analysis, and gel retardation assays. In vitro studies were performed on HRNB cells using resazurin assays for cytotoxicity. In vivo targeting was assessed in NSG mice using Cy5-labeled polyplexes and imaged with the LagoX system.

Results: The resulting PBA-PNPs exhibited a uniform nanoscale size with high colloidal stability over one week. Under reductive conditions mimicking the intracellular tumor environment, the nanoparticles disassembled, facilitating miR release. Confocal imaging of HRNB cells demonstrated that PBA-functionalization led to a 90% increase in cellular uptake compared to non-targeted PNPs, suggesting GD2-mediated intra-cellular delivery. Notably, our platform maintained high cell viability (~100%), demonstrating minimal carrier-related toxicity. When loaded with tumor-suppressive miR-124, PBA-PNPs exhibited increased HRNB cell killing compared to non-targeted PNP controls. In vivo studies using an HRNB mouse model demonstrated increased tumor accumulation of PBA-PNPs, validating their targeting efficacy.

Conclusion: These results present a rationally designed nanocarrier system that integrates GD2-targeting and redox-dependent release for precision miR therapy. This modular approach highlights the potential of PBA-PNPs as a promising delivery system for miRNA therapeutics in pediatric oncology.

2-B TARGETING LYSOSOMAL AUTOPHAGY WITH BAQ42, A NOVEL BISAMINOQUINOLINE DERIVATIVE, FOR THE TREATMENT OF TRIPLE-NEGATIVE BREAST CANCER

Athena Aragon, Graduate Student^{1,2}, Menghuan Tang^{1,2}, Qiufang Zong¹, Francisco Castaneda¹

¹Department of Biochemistry and Molecular Medicine, UC Davis, Sacramento, CA; ²UC Davis Comprehensive Cancer Center, Sacramento, CA

Triple-negative breast cancer (TNBC) is among the most aggressive breast cancer subtypes due to its lack of hormone receptors, fast growth, and high recurrence. TNBC accounts for 12% of breast cancers, with a five year survival rate as low as 10-15% in metastatic cases. Standard treatment remains largely limited to chemotherapy, surgery, and radiation, yet relapse rates and metastatic survival remain poor, in part because cancer cells rely on multiple protective mechanisms to survive treatment. Autophagy, a lysosome-dependent process used to survive therapeutic and metabolic stress, is one such mechanism, and has become a promising therapeutic target. This reliance on autophagy is sometimes called the "Achilles' heel" of cancer: cancer-associated lysosomes are more numerous, morphologically distinct, and more active than normal lysosomes, supporting rapid tumor growth, yet this same upregulation leaves them more fragile and selectively vulnerable to induced membrane permeabilization.

This lysosomal fragility has led researchers to repurpose existing lysosomotropic drugs for cancer treatment. Among these are hydroxychloroquine (HCQ) and its parent compound chloroquine (CQ), FDA-approved antimalarials now investigated as autophagy inhibitors, which have shown preclinical promise in TNBC by reducing tumor stem cell populations and sensitizing cells to chemotherapy. However, while preclinical results have been largely positive, clinical trial outcomes have been inconsistent. This is due in part to CQ/HCQ's limited potency as autophagy inhibitors, dose-limiting toxicity, and lack of specificity, as they also cause autophagy-independent, off-target effects. More potent, more specific lysosomotropic agents are needed.

Here, we show that BAQ42, a novel bisaminoquinoline derivative developed in our lab, is a more effective autophagy inhibitor than HCQ, driving greater lysosomal disruption and tumor cell apoptosis. In vivo, BAQ42 treatment significantly suppressed tumor growth and extended survival in both orthotopic and spontaneous transgenic models of breast cancer, with the transgenic model additionally confirming stable body weight and BAQ42 localization to primary tumors and metastasis. Together, these findings position BAQ42 as a next-generation autophagy inhibitor with strong potential for TNBC therapy.

3-A PHOTOACOUSTIC TRACKING OF NANOENGINEERED NK CELLS IN COMBINATION WITH RADIOTHERAPY

Brendan Barlow, Graduate Student^{1,3}, Tasneem Mukarrama^{1,3}, Megan Purfi^{1,3}, Alexander Lebea²

¹Department of Surgery, UC Davis, Sacramento, CA; ²Department of Radiation Oncology, UC Davis, Sacramento, CA; ³UC Davis Comprehensive Cancer Center, Sacramento, CA

Introduction: Adoptive Natural Killer (NK) cell therapy shows promise as an off-the-shelf cancer immunotherapy, but critical in vivo behaviors like homing and persistence after infusion remain poorly characterized. While radiotherapy (RT) combined with NK cell therapy enhances efficacy, optimal timing and dose of neoadjuvant RT remains unclear. To address this, we engineered NK cells labeled with nanoparticles (NPs) that generate photoacoustic signals detectable under multi-wavelength ultrasound/photoacoustic (US/PA) imaging. Here, we

evaluated the impact of NP labeling on NK cell function and characterized the photoacoustic (PA) properties of labeled cells.

Methods: Poly(lactic-co-glycolic) acid (PLGA) NPs containing indocyanine green (ICG) were synthesized and used to label human NK cells at multiple concentrations. We assessed labeling effects on expression markers, viability, migration, and cytotoxicity against several cancer cell lines. PA signal generation was demonstrated in vitro by comparing signal strength between labeled and unlabeled NK cells. For in vivo tracking, labeled NK cells were injected into NSG mice bearing human A673 Ewing sarcoma tumors. One group received focal RT (8 Gy) 18 hours before injection; another received no RT. Tumors were US/PA imaged before and after adoptive transfer, and PA signal intensity was quantified.

Results: PLGA NP labeling did not significantly affect NK cell surface marker expression, viability, migration, or cytotoxicity relative to unlabeled controls. Using both NK-92 and placenta-derived primary NK cells, functional assays showed no significant differences between labeled and unlabeled groups. In tissue-mimicking phantoms, labeled NK cells generated markedly higher PA signals than unlabeled cells. In vivo, saline-treated control mice showed no detectable PA signal despite clear tumor anatomy on US, while mice receiving labeled NK cells showed notable tumor accumulation post-transfer. Mice receiving RT prior to NK cell injection showed significantly higher PA signal than those without RT, indicating RT enhanced NK cell homing to tumors.

Conclusions: Nanoengineering NK cells with PLGA NPs preserves cell function while enabling robust, distinguishable PA signals for in vivo tracking. Combined with RT, this approach offers strong potential for optimizing RT timing and dosing based on real-time NK cell tracking. Future integration with functional activity monitoring may further improve NK cell therapy optimization.

4-B NIMBOLIDE SUPPRESSES MIGRATION OF CANINE TCC CELLS BY PREVENTING EMT VIA RHOJ DOWNREGULATION

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Background: Treatment options for dogs with bladder cancer (BICa) (mostly Transitional Cell Carcinoma (TCC)) include non-steroidal anti-inflammatory drugs (NSAIDs) such as piroxicam, and chemotherapy, with is non-curative but carries health risks. This highlight the need for safe, affordable, and effective therapies for canine TCC. Nimbolide, a limonoid isolated from *Azadirachta indica* (Neem) leaves, has demonstrated anti-tumor activity in human BICa but has not been tested in canine TCC.

Methods: Canine cell lines K9TCC-PU-AXC and K9TCC-PU-Pu, were used. Cell viability was estimated in 2D by MTT and in 3D by live/dead cell staining, cell cycle progression and apoptosis by flow cytometry, cell migration by wound healing assay, epithelial mesenchymal transition (EMT) by the expression of Vimentin, Snai-1, Snai-2, E- and N-cadherin. Immunoblotting and immunofluorescence determined protein expression. RNA-seq estimated gene expression validated by qPCR. Immunohistochemistry analyzed tumors from dogs with TCC. Knockdown of RhoJ was accomplished by siRNA.

Results: Nimbolide suppressed cell growth via G2/M arrest and triggered autophagy-mediated death, inhibited cell migration and suppressed EMT markers including the intermediate filament protein, Vimentin. RNA-sequencing showed nimbolide significantly downregulated RhoJ, which regulates cell migration. RhoJ expression was detected in tumor tissue from 23 dogs with TCC. RhoJ was predominantly cytoplasmic in tumors from male dogs (8/12), and primarily membranous in female tumors (6/10) (p=0.0427). Treatment with piroxicam shifted RhoJ localization from the cytoplasm to the membrane (4/5) compared to those with no treatment (0/6) (p=0.0327), whereas chemotherapy did not have such an effect (4/11). In addition, RhoJ expression was detected in stromal cells, and elevated stromal RhoJ expression was associated with disease progression (HR=18.9, p=0.009). Knockdown of RhoJ prevented nimbolide-induced downregulation of Vimentin and increased E-cadherin.

Conclusions: The above indicate that nimbolide suppresses migration of canine TCC cells by preventing EMT via RhoJ downregulation. Based on these results, we intend to develop nimbolide as a therapeutic tool in the treatment of canine TCC in future studies.

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5-A PRODUCTION AND PURIFICATION OF NOVEL BIOENGINEERED MIR-1291-5P AGENT FOR CANCER RESEARCH

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MicroRNAs (miRNAs, miRs) serve as key post-transcriptional regulators of gene expression in various cellular processes that may impact disease initiation and progression. Our previous research has shown that microRNA-1291-5p (miR-1291-5p) is able to suppress pancreatic cancer progression via targeting oncogenes, controlling cell metabolism, and sensitizing cells to chemotherapy in vivo and in vitro, demonstrating its therapeutic potential. Current RNA-based research and drug development predominantly rely on chemically synthesized mimics, which contain extensive artificial modifications that alter features relative to those of natural RNA. The aim of the current study was to produce and purify biological miR-1291-5p using the novel glycyl-tRNA-fused pre-miR-34a carrier (BioRNAGly/miR-1291-5p, BioRNA/miR-1291) to better recapitulate the structure, function, and safety of natural RNAs for functional studies. Specific primers were designed to amplify the coding sequence of BioRNA/miR-1291. Following cloning and sequence validation, BioRNA expression plasmids were transformed into HST08 *Escherichia coli* cells and incubated for varying timeframes. The results showed that BioRNA/miR-1291 achieved high-level heterologous expression (> 40% of total RNA), with 7.5 mg, 13.6 mg, 13.5 mg, and 10.6 mg of total RNA isolated from each 100 mL culture at 12-, 14-, 16-, and 18-h culture, respectively. Total RNA was then purified using an anion exchange fast-protein liquid chromatography (FPLC) method, with the highest yielding time points being 14- and 16-h, at approximately 5.5 mg. Final BioRNA purity was determined semi-quantitatively by denaturing urea-polyacrylamide gel electrophoresis (PAGE) and quantified by high-performance liquid chromatography (HPLC), with all products achieving > 99% purity. This study establishes an optimal method for the production of highly pure BioRNA/miR-1291, providing reliable insight into the effects of varying incubation time during BioRNA production for cancer therapeutic research and drug discovery.

6-B TREATING DRUG-TOLERANT PERSISTENT CELLS IN TRIPLE-NEGATIVE BREAST CANCER WITH THE NOVEL AUTOPHAGY INHIBITOR BAQ42

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Triple-negative breast cancer (TNBC) accounts for 10–20% of all breast cancer cases, with a recurrence rate of 30–40% within the first 3–5 years after initial treatment. This recurrence is associated with resistant, stem-like cancer cell populations that survive therapeutic stress by entering a reversible, slow-cycling state before resuming proliferation once therapy is withdrawn. These treatment-resistant, stem-like populations, commonly referred to as drug-tolerant persister (DTP) cells, are also associated with increased invasiveness and poorer prognosis in TNBC patients.

DTP cells exhibit specific therapeutic vulnerabilities linked to shifts in metabolic and stress-response pathways that enable their survival. Among these, elevated autophagy-lysosomal activity has been widely reported in DTP cells, helping sustain the mitochondrial reactive oxygen species (mROS) levels linked to their survival and chemotherapy resistance. Targeting this dependency may therefore represent a promising strategy to selectively eliminate DTP cells, addressing a key gap given that existing TNBC therapies fail to eliminate these populations.

Chloroquine (CQ), an FDA-approved antimalarial being investigated as an autophagy inhibitor, has shown promise against TNBC cancer stem cells in cell culture studies. Its derivative, hydroxychloroquine (HCQ), is also FDA-approved and is currently being tested in clinical trials for TNBC. However, both compounds have produced inconsistent tumor responses, and both require large doses to be effective — resulting in side effects such as retinal toxicity, cardiomyopathy, and hypoglycemia that remain a key limitation to their clinical use.

Our work demonstrates that BAQ42, a novel bisaminoquinoline developed in our lab, is a more on-target autophagy-lysosomal inhibitor than HCQ. DTP cells exhibit greater resistance to Paclitaxel (PTX) and HCQ than parental cells; however, BAQ42 retains potent cytotoxic activity against DTP cells and is significantly more toxic to this resistant population than either PTX or HCQ. BAQ42 also reduces expression of stem cell markers in DTP cells to below parental cell levels, showing the potential to target the population responsible for TNBC recurrence and invasiveness. Together, these results identify BAQ42 as a more targeted and effective autophagy inhibitor, with the potential to eliminate DTP cell populations and reduce recurrence in patients with TNBC.

7-A LOSARTAN IN COMBINATION IMMUNOTHERAPY WITH PD-1/PD-L1 BLOCKADE TO TARGET OLIGOMETASTATIC HEAD AND NECK CANCER

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Immune checkpoint inhibitors (ICI) targeting PD-1/PD-L1 are the frontline treatment for recurrent and metastatic head and neck squamous cell carcinoma (HNSCC), but response rate and survival remain limited. Angiotensin II type 1 receptor blockers (ARBs) like Losartan may remodel tumor microenvironment (TME) stroma and target TGF- β -mediated myeloid cell activities to improve ICI response. This study sought to assess immune cell populations within TME, evaluate plasma cytokines, and measure plasma TGF- β 1 of Losartan-treated mouse model of HNSCC. Mouse model of HNSCC was generated via flank injection of murine SCC cells derived from keratin 15+ stem cells harboring a KrasG12D mutation and Smad4 deletion. Mice were treated with or without RT (8 Gy), anti-PD-L1 (250 μ g intraperitoneal (IP) once every 2 days for 6 treatments), and Losartan (60 mg/kg IP once a day). Formalin-fixed paraffin-embedded primary tumors were assessed via immunohistochemistry for macrophages, neutrophils, CD8 T cells, and NK cells, and for cytotoxicity by granzyme B. Plasma was assessed via cytokine array and TGF- β 1 ELISA. Treatment with Losartan maintained CD8 T cell infiltration and improved CD8 T cell cytotoxicity within TME as compared to treatment with only anti-PD-L1 and RT. Treatment with Losartan also increased NK cell infiltration and cytotoxicity within TME. Losartan in combination with PD-1/PD-L1 ICI and RT resulted in improved immune cell infiltration and cytotoxicity within TME. Further investigation of effects of Losartan on TGF- β -mediated immune cell activities and TME stromal remodeling are warranted to characterize the role of ARBs in immunotherapeutic strategies for HNSCC.

8-B EXPANSION OF TISSUE RESIDENT CXCR6+ T CELLS IN RESPONSE TO PANCREATIC ADENOCARCINOMA LIVER METASTASES INFORMS CELLULAR THERAPY DESIGN

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Introduction: Liver metastases are an important driver of mortality in pancreatic ductal adenocarcinoma (PDAC). While CAR T cells have shown exceptional results in hematologic malignancies, success against solid tumors, including metastatic PDAC, has been limited by challenges with trafficking and engrafting within metastatic sites. To inform CAR T design against PDAC liver metastasis, we characterized the phenotypic changes of liver T cells within the metastasis-bearing liver by measuring expression of tissue residency/adhesion markers in a syngeneic murine model of PDAC liver metastasis.

Methods: PDAC metastatic to liver was modeled by injecting 10⁶ PAN02-luciferase cells via hemi-spleen into syngeneic C57BL/6 mice. Tumor burden was monitored using bioluminescent imaging (BLI). Six weeks post-injection, tumor-bearing and matched-control mice were euthanized for liver T cell analysis, including T cell subsets and memory/tissue residency markers, by multicolor flow cytometry.

Results: At six-week endpoint, liver tumors (BLI and necropsy) of 3 mice and 3 control mice were collected and analyzed. CD3+ and CD4 T cell counts in bulk liver tissue were not significantly different between tumor-bearing and control livers. There was an enrichment of effector memory (CD44+/CD62L-) CD8 T cells (48% +/- 7.5% vs. 21 +/- 2.9%, $P < 0.001$) and a reduction in naïve (CD44-/CD62L+) CD8 T cells (34% +/- 11% vs. 66% +/- 2.5%, $P < 0.001$) in the tumor-bearing livers compared to control livers. Expression of CXCR6 in effector memory (94% +/- 3.3% vs. 75% +/- 9.3%, $P = 0.004$) and effector (CD44-/CD62L-) (78% +/- 9.4% vs. 36% +/- 6.8%, $P < 0.001$) CD8 T cell subsets also had

significantly greater expression in tumor-bearing livers compared to controls.

Conclusion: In this syngeneic PDAC liver metastases model, there is enrichment of effector memory and effector CD8 T cells within the liver, which display a significant increase in tissue resident marker CXCR6. CXCR6 expression has been linked to recruitment and retention of cytotoxic T cells within liver tumor tissue, and our results suggest that CXCR6 modulation may represent a liver-specific T cell response to PDAC metastases. Augmenting CXCR6 expression on CAR T cells against PDAC may have improved function against metastatic sites, including the liver.

9-A IMPROVING TREATMENT VOLUME ESTIMATION WITH CONE-BEAM CT IN YTTRIUM-90 RADIOEMBOLIZATION

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Introduction: Cone-beam computed tomography (CBCT) is widely used for pretreatment planning in Yttrium-90 (⁹⁰Y) radioembolization to assess tumor volume, a critical parameter for activity and dose calculation. However, CBCT-derived volumes may differ from those obtained by post-treatment PET/SPECT, the reference standard for assessing activity distribution, with potentially important implications for dose prescription. This discrepancy remains poorly characterized, particularly for small-volume tumors. This study aims to quantify CBCT-PET/SPECT volume differences, identify factors contributing to these discrepancies, and establish practical strategies to improve CBCT-based pretreatment planning.

Methods: Imaging data from 41 ⁹⁰Y patients was retrospectively analyzed. Pretreatment CBCT images were acquired during angiography mapping. Post-treatment volumes were segmented on PET/CT or SPECT/CT images using MIM Encore™ with three methods: Region Grow, PET Edge, and fixed-Threshold. Patients were stratified into small-volume (≤ 200 cm³) and large-volume (> 200 cm³) cohorts. CBCT-PET/SPECT agreement was evaluated using linear regression and Bland–Altman analysis. Absolute volume and percentage discrepancies were compared between cohorts to assess whether disagreement magnitude varied by CBCT-derived volume.

Results: All three segmentation methods showed strong CBCT-PET/SPECT volumes correlation (Spearman $\rho = 0.887$ – 0.901 , $R^2 = 0.928$ – 0.932), indicating excellent agreement. However, CBCT systematically underestimated volumes across methods: Region Growing (bias = 85.86 ± 71.14), PET Edge (bias = 82.03 ± 69.86), and Threshold (bias = 88.69 ± 70.18). Critically, the absolute percentage discrepancy was greater in the small-volume cohort than in the large-volume cohort (Welch's t-test, $p < 0.001$), supporting the hypothesis that discrepancies between CBCT and PET/SPECT volumes are greater in smaller treatment volumes.

Conclusion: When CBCT-derived volumes are used directly for treatment planning, the systematic 80–88 cm³ underestimation results in lower prescribed activity and absorbed dose than intended. For example, a CBCT-measured 100-cm³ tumor would correspond to an actual volume of 180–188 cm³ and receive only 53–56% of the intended dose. Thus, a patient intended to receive 205 Gy would instead receive 109–115 Gy, potentially compromising tumor control. To address this, CBCT-derived volumes should be systematically increased by 80–88 cm³ before activity calculation, or PET/SPECT-based dose thresholds should be translated to equivalent CBCT-based values.

10-B THE IMPOSTER WITHIN: TALL CELL CARCINOMA WITH REVERSE POLARITY, A RARE BREAST CANCER WITH HISTOLOGIC SIMILARITIES TO THYROID CANCER

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Background: TCCRP is a rare subtype of breast cancer that is often triple negative but indolent and rarely metastatic. Unlike other triple negative breast cancers, neoadjuvant chemotherapy is not recommended for this type of breast cancer, and sentinel lymph node biopsy is usually unnecessary. We share 3 unique cases of the disease that we have encountered at our institutions in the past 5 years.

Sample Case: 68-yo F with a palpable left breast mass presented for diagnostic evaluation. Core biopsy pathology showed tall columnar cells with nuclei lined up along the luminal aspect of the cell consistent with diagnosis of TCCRP. Patient underwent left breast partial mastectomy.

Discussion: On imaging, the disease shares similar features to papillary lesions and TNBC. The pathologic appearance is similar to papillary carcinoma of the thyroid gland.

Conclusion: Although rare, it is important to keep the diagnosis of tall cell carcinoma with reverse polarity in the differential diagnosis for a patient presenting with a breast mass. This indolent malignancy is treated less aggressively than other similar appearing breast cancers and has an excellent prognosis.

11-A INTEGRATING 3D-BIOPRINTED TUMOROID DRUG SCREENING AND HISTOLOGIC MORPHOMETRIC BIOMARKERS IDENTIFIES NIMBOLIDE SUSCEPTIBILITY AND MECHANISM IN BLADDER CANCER

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Nimbolide is a neem-derived limonoid with reported anticancer activity, but the tumor phenotypes associated with nimbolide susceptibility and its mechanisms of action in bladder cancer remain incompletely understood. We combined patient-derived 3D-bioprinted tumoroid drug screening with computational morphometric analysis of tumor histology to identify nimbolide-responsive tumors and determine the biological programs underlying treatment response.

Patient-derived bladder cancer tumoroids were evaluated against nimbolide and clinically relevant therapies using a functional response score integrating growth inhibition and cytotoxicity. Nimbolide emerged as one of the most efficacious treatments evaluated across the cohort, including in comparison with standard-of-care agents. To identify a histologic phenotype associated with response, correlation structures among 256 cellular morphometric biomarkers were defined in an outcome-blind reference cohort. These frozen morphometric modules were subsequently tested against nimbolide functional response data from matched patient-derived tumoroids.

This analysis identified a 26-feature morphometric program, Module 4, associated with nimbolide sensitivity. Module 4 was then mapped into 386 bladder tumors from The Cancer Genome Atlas and integrated with matched RNA-sequencing data. Tumors expressing the nimbolide-susceptible morphometric phenotype demonstrated transcriptional programs involving mitochondrial dysfunction, oxidative and redox stress, ferroptotic vulnerability, and immune signaling.

These computationally predicted mechanisms were evaluated experimentally using quantitative PCR, Seahorse metabolic analysis, immunofluorescence imaging, and cytokine and chemokine profiling. Nimbolide treatment caused mitochondrial relocalization of HMOX1, reduced ATP-linked oxygen consumption, increased lipid peroxidation and intracellular iron, and inhibited GPX4 activity, supporting a mitochondrial and ferroptotic mechanism of tumor injury. Nimbolide also increased CXCL10 and extracellular DNA release without producing broad IFN- γ activation, suggesting that tumor damage may generate selective immune-recruitment signals rather than generalized immune activation.

Together, these findings demonstrate that functional response measurements from 3D-bioprinted patient tumoroids can be coupled with histology-derived morphometric biomarkers to identify treatment susceptibility, interrogate large transcriptomic cohorts, and predict drug mechanisms that can be independently validated in the laboratory. This integrated strategy provides a scalable framework for discovering and mechanistically characterizing candidate cancer therapies using routinely available tumor histology.

12-B A COMBINATION TREATMENT STRATEGY WITH A LUTETIUM-177 LABELED INTEGRIN AVB6-TARGETING PEPTIDE AND OLAPARIB IN A PANCREAS CANCER MOUSE MODEL

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The integrin $\alpha\beta 6$ is an epithelial specific cell surface receptor that is overexpressed on numerous malignancies including pancreatic ductal adenocarcinomas (PDAC), making it a promising molecular target for the detection and treatment of many cancers. We have previously demonstrated that our $\alpha\beta 6$ -targeted Peptide Receptor Radionuclide Therapy (PRRT) agent, [¹⁷⁷Lu]Lu-DOTA-ABM-5G (177Lu-1) increased survival of mice bearing pancreatic cell xenograft tumors, and it is currently being evaluated in a Phase-1 clinical trial in patients with metastatic or locally advanced pancreatic ductal adenocarcinoma (NCT04665947). With the goal to further enhance its therapeutic efficacy, here we combine 177Lu-1 with an FDA approved poly (ADP-ribose) polymerase (PARP) inhibitor Olaparib. The combination was evaluated in vitro for cell binding, cell viability, cell cycle arrest and the formation of double-strand breaks in $\alpha\beta 6$ (+) human pancreatic cancer cell line Capan-1. Pharmacokinetics of 177Lu-1 and therapeutic efficacy (Groups: 1-Saline, 2- Olaparib, 3- 177Lu-1, and 4- Olaparib + 177Lu-1) was evaluated in mice bearing Capan-1 tumors xenografts. Rapid cell binding (52% at 1 h) and internalization (>78% of bound at 1 h) of 177Lu-1 was observed in Capan-1 cells. In the WST-1 assay, the combination 177Lu-1 + Olaparib resulted in a significant decreased cell viability, significant increase in the percentage of cells in the sub-G1 and G2/M phases, and resulted in the greatest number of γ -H2AX foci per cell compared to single agent treatment. The biodistribution study demonstrated uptake and slow washout over time of 177Lu-1 in the Capan-1 tumor (percentage of injected dose per gram, % ID/g: 4.4 $\pm$ 0.5% ID/g at 4 h and 3.4 $\pm$ 0.3% ID/g at 72 h). In a therapeutic efficacy study, tumor growth was significantly slowed for the first 17 days post treatment for treatment Groups 2-4, most notably for the combination Group 4 compared to the saline group that showed rapid growth. The median survival of Groups 1, 2, 3 and 4 were 28, 37, 44, and 65 d, respectively. No treatment related adverse events were noted. In conclusion the combination of $\alpha\beta 6$ -targeted PRRT and PARP inhibition enhanced therapeutic efficacy compared to either single agent treatment.

13-A UTILIZING TUMOROIDS GENERATED FROM HEAD AND NECK SQUAMOUS CELL CARCINOMA TO EVALUATE TUMOR INFILTRATING LYMPHOCYTE CELLULAR THERAPY

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Head and neck squamous cell carcinoma (HNSCC) has a dismal prognosis after metastasis, with a median overall survival of 10 months. Most patients fail or develop resistance to standard-of-care immune checkpoint inhibitors (ICIs) and chemotherapy, highlighting the need for more effective strategies. Tumor infiltrating lymphocytes (TIL) are a cellular therapy in which T cells are isolated from patient tumors, expanded ex vivo, and re-infused into the patient. Though promising for metastatic melanoma, TIL therapy had an 11% overall response rate in HNSCC patients. This disparity may reflect the immunosuppressive tumor microenvironment (TME) of HNSCC. Here, we utilized a novel patient-derived, 3D-bioprinted tumoroid system generated from oral squamous cell carcinoma (OSCC) tissue to evaluate interactions between autologous TIL and the TME ex vivo. By incorporating tumor cells with patient-derived stromal components within a three-dimensional hydrogel, the platform preserves cellular and extracellular hallmarks of the native TME, recapitulating features that are not maintained in two-dimensional cultures.

TIL were generated from OSCC by dissociation and digestion of the tumor. Subsequently, T cells were selectively expanded with CD3 stimulation and IL-2. Differentiation and exhaustion phenotypes of the TIL were characterized by flow cytometry. Differentiation status was determined by expression of CD45RA, CD62L, CD95, CD28, and CD27. Differentiation state, including the proportion of terminally differentiated and T stem cell memory (Tscm) cells, varied among patients, as did expression of exhaustion markers PD-1, LAG3, and TIM3. Tumoroids were generated by digestion of OSCC tissue into a viable single-cell suspension which was fluorescently labeled for tracking, incorporated into a collagen-based hydrogel, and bioprinted into 3D constructs. Tumoroids were co-cultured with autologous TIL or peripheral blood mononuclear cells (PBMCs), with or without the ICIs pembrolizumab and durvalumab, using a 30:1 effector-to-tumor cell ratio. High-content imaging was used to quantify tumor-cell growth and viability, immune-mediated cytotoxic and cytostatic effects, and effector-cell infiltration. Culture supernatants were analyzed for IFN- γ by ELISA as an orthogonal measure of T cell reactivity. Together, these studies establish a functional, patient-derived 3D tumor-immune platform for evaluating OSCC-TME interactions, enabling ex vivo testing of therapeutics to overcome tumor-mediated immune suppression and improve TIL-based therapy for HNSCC.

14-B FEASIBILITY OF IMPROVING THE Y-90 SIRT WORKUP USING PERFUSION CT: A PHANTOM STUDY

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Introduction: More than 10,000 liver cancer patients in US undergo yttrium-90 selective internal radiation therapy (Y-90 SIRT) each year. However, the current invasive planning workup is lengthy and costly, requiring separate cone-beam CT (CBCT) and SPECT acquisitions to plan the delivered dose and determine patient eligibility. This study investigated the feasibility of developing a simplified, image-based approach for estimating hepatic blood flow and Y-90 microsphere distribution using perfusion CT.

Methods: An experimental phantom dataset was acquired using a CT scanner with one acquisition per second during the injection and transport of an iodinated contrast solution (Figure 1). Contrast transport was described mathematically using the advection-diffusion equation. The corresponding velocity field and diffusion coefficient, both assumed time independent, were estimated by optimizing the model against a time series of measured contrast concentration distributions. The optimized parameters were then used to reconstruct the concentration distributions, which were compared with the reference measurements at multiple time points.

Results: The reconstructed concentration distributions closely reproduced the spatial and temporal evolution of the reference measurements over nine consecutive 1-s time steps (Figure 2). Even after nine sequential updates, the MRAE remained below 10%, demonstrating the model's ability to maintain good agreement over time. Larger relative errors were primarily confined to the distribution boundaries, where low reference concentrations amplified the relative errors.

Discussion: These phantom results demonstrate the feasibility of estimating the contrast-agent transport from dynamic CT measurements using an advection-diffusion model. With further validation, this approach could help predict intrahepatic Y-90 microsphere distribution for different injection locations and feasibly support treatment-planning optimization. Validation using numerical phantoms with known ground-truth velocity and diffusion fields, followed by evaluation using patient data, is required.

Conclusion: These preliminary findings demonstrate the feasibility of combining perfusion CT with advection-diffusion modeling to reconstruct contrast-agent transport, supporting its potential as an approach for improving the Y-90 SIRT workup.

15-A TUMOR-TARGETED NANOPARTICLE TRI-THERAPY INDUCES DURABLE ANTITUMOR IMMUNITY THROUGH COORDINATED MYELOID AND T-CELL REPROGRAMMING

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Although immune checkpoint blockade has transformed cancer therapy, many solid tumors remain immunologically “cold,” with insufficient antitumor immune responses that limit therapeutic efficacy. Strategies that simultaneously induce tumor destruction and activate antitumor immunity may help overcome this resistance. Here, we developed a tumor-targeted nanotherapy strategy integrating chemotherapy, innate immune stimulation, and PD-1 blockade to promote tumor regression and durable antitumor immunity. In the syngeneic MB49 bladder cancer model, a PLZ4-targeted PVA–porphyrin–catechol nanoparticle (PPCN) was used to deliver doxorubicin and the Toll-like receptor 7/8 agonist R848 in combination with systemic anti-PD-1 therapy. Therapeutic efficacy and antitumor immunity were evaluated by tumor response, rechallenge, flow cytometry, IFN- γ ELISPOT, and tumor gene-expression analysis. PPCN-mediated tri-therapy achieved complete tumor regression in 12 of 14 mice (86%), compared with 2 of 7 mice receiving PPCN-delivered doxorubicin and R848 without PD-1 blockade. All evaluated complete responders (7/7) rejected subsequent tumor rechallenge without additional treatment, demonstrating durable antitumor protection. Tri-therapy increased intratumoral CD3⁺ T-cell infiltration more than two-fold compared with saline controls (50.2% vs. 21.7%) and enhanced CD8⁺ T-cell activation, as indicated by increased CD25 expression (47.7% vs. 13.6%). Treatment also remodeled tumor-associated myeloid populations toward a more inflammatory phenotype, characterized by increased CD86 expression in Ly6C⁺ inflammatory myeloid cells and reduced CD206 expression in Ly6C⁺ populations. Rechallenged mice exhibited enhanced tumor-responsive IFN- γ production (117.8 vs. 10.0 SFU/10⁶ T cells in naïve controls), accompanied by increased expression of memory-associated genes including Tcf7, Lef1, and Il7r. These findings demonstrate that tumor-targeted chemotherapy and innate immune stimulation can cooperate with PD-1 blockade to remodel the tumor immune microenvironment and generate durable, memory-forming antitumor immunity.

16-B NOVEL APPROACH TO TRIPLE-NEGATIVE BREAST CANCER USING A FIRST-IN-CLASS PIP5K1B INHIBITOR AS A STRATEGY TO SUPPRESS PI3K/AKT

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Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype with limited targeted therapies and high metastatic potential. PIP5K1 has three isoforms, α , β , and γ , and is involved in PI3K/AKT signaling. While inhibitors targeting the α and γ isoforms have been investigated, no FDA-approved inhibitor specifically targets PIP5K1 β . This study evaluates SMI-299, a novel small-molecule inhibitor targeting PIP5K1 β , as a potential therapeutic strategy for TNBC. MDA-MB-231 TNBC cells were treated with SMI-299 to evaluate cell viability, dose-response and IC50, migration, invasion, and changes associated with PI3K/AKT signaling. In addition to conventional 2D monolayer culture, a 3D tumor model such as spheroids was used to compare treatment responses and determine whether a more tumor-like cellular environment alters the observed efficacy of SMI-299.

SMI-299 showed anti-tumor activity in MDA-MB-231 cells, including reduced cell viability and suppression of aggressive cancer-associated behaviors. Comparison of 2D and 3D models provided additional information on drug response, with the 3D model offering a more biologically relevant assessment of SMI-299 activity, showing decreased metastatic behavior in the spheroids, reduced invasion, and

migration. These findings support PIP5K1 β as a potential therapeutic target for TNBC and suggest that 3D models may provide a more physiologically relevant platform for evaluating SMI-299 before further in vivo studies.

17-A BIOENGINEERED MIR-124 AND MIR-34A ENHANCE CISPLATIN RESPONSE IN HIGH-RISK NEUROBLASTOMA

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Introduction: High-risk neuroblastoma (HRNB) remains a major cause of cancer-related mortality in children despite intensive multimodal therapy. Platinum-based chemotherapy is a cornerstone of HRNB treatment, but its clinical utility is limited by substantial acute and long-term toxicities. We investigated whether bioengineered miR-124 and miR-34a (bioRNAs) could enhance cisplatin efficacy through complementary molecular mechanisms and enable effective tumor control at reduced chemotherapy doses.

Methods: The therapeutic effects of bioengineered miR-124 and miR-34a, alone and in combination with cisplatin, were evaluated across molecularly distinct HRNB cell lines. Cell viability and apoptosis were assessed following bioRNA-cisplatin co-treatment, and drug interactions were evaluated for synergistic effects. Quantitative proteomic analyses were performed to identify bioRNA-regulated molecular pathways and potential mechanisms underlying enhanced cisplatin sensitivity. Therapeutic efficacy was further evaluated in SK-N-SH, Be(2)-C, and NB1643 xenograft models by comparing bioRNA monotherapy, cisplatin monotherapy, and bioRNA-cisplatin combination treatment.

Results: Both bioRNAs significantly suppressed neuroblastoma cell viability through distinct biological programs. Proteomic analyses revealed that miR-124 preferentially promoted neuronal differentiation, whereas miR-34a predominantly activated apoptotic pathways. Combination treatment produced robust synergistic interactions with cisplatin across multiple HRNB cell lines and suppressed proteins involved in nucleotide excision repair and homologous recombination-mediated DNA damage repair. BioRNA-cisplatin co-treatment further enhanced apoptosis while promoting differentiation-associated phenotypes. In vivo, both bioRNAs suppressed tumor growth as monotherapies, with the strongest responses observed in combination with low-dose cisplatin. Across all three xenograft models, combination therapy reduced tumor burden, induced extensive tumor necrosis, and achieved complete tumor regression in a subset of animals. Importantly, low-dose cisplatin combined with bioRNA therapy frequently achieved tumor control comparable to or greater than higher-dose cisplatin monotherapy while maintaining favorable tolerability.

Conclusion: Bioengineered miR-124 and miR-34a are potent cisplatin sensitizers that enhance platinum responsiveness through complementary differentiation- and apoptosis-associated mechanisms and modulation of DNA damage repair pathways. These findings support bioRNA-based combination therapy as a promising strategy to improve HRNB treatment while reducing chemotherapy-associated toxicity.

18-B ELTROMBOPAG SAFETY IN PEDIATRIC SOLID TUMORS RECEIVING INTENSIVE CHEMOTHERAPY

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Background: Pediatric cancers account for less than 1% of annual cancer diagnoses, yet they remain the leading cause of disease-related mortality in children. Myelosuppression post chemotherapy can lead to severe and prolonged thrombocytopenia (< 10,000), causing increased bleeding risk, requiring platelet transfusions and associated complications, and delays in therapy that could compromise outcomes. Eltrombopag, an oral thrombopoietin receptor agonist, is effective in treating pediatric thrombocytopenic disorders such as immune thrombocytopenic purpura (ITP) and aplastic anemia, but it has not been evaluated in children receiving upfront myelosuppressive chemotherapy.

Objectives: To evaluate (1) the safety of eltrombopag in pediatric patients undergoing intensive chemotherapy for malignant solid tumors, (2) the efficacy of eltrombopag in supporting platelet recovery in this population and reducing need for platelet transfusions.

Methods: A total of 9 patients aged 1-18 years old were enrolled in the study between 2021-2025. Patients received eltrombopag on the first day following the completion of chemotherapy and continued until 2 days prior to next chemotherapy cycle or a rise in platelet counts to 150,000/ μ L, whichever occurred first. Safety monitoring was conducted throughout the study period as defined on the study calendar. All outcomes were analyzed using descriptive methods due to the pilot design and small sample size.

Results: Of the 9 patients (median age: 8.9, range 13 months-18 years), 7 patients with solid tumors received eltrombopag for an average of 2 chemotherapy cycles (range 1-4 cycles). Two patients were initially eligible but could not start eltrombopag because platelets exceeded the <150K threshold on the designated start day. Platelet count increases were observed in individual patients during eltrombopag administration, including one patient with a rise from 7,000/ μ L to 532,000/ μ L, without associated adverse events. No serious adverse events were attributable to eltrombopag.

Conclusion: Eltrombopag is safe and feasible to administer in children receiving intensive chemotherapy for solid tumors. In this pilot study, patients who did not initiate eltrombopag due to platelet thresholds subsequently developed thrombocytopenia nadir, highlighting the limitations of threshold-based initiation. Future studies should consider administering the drug shortly after completion of chemotherapy despite normal platelet counts.

19-A STEM CELL MEMBRANE-POLYMER HYBRID NANOVESICLES FOR TARGETED MIRNA DELIVERY IN HIGH-RISK NEUROBLASTOMA

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Introduction: High-risk neuroblastoma (HRNB) is a pediatric solid tumor with high tumor heterogeneity and a substantial risk of relapse, highlighting the need for improved therapeutic strategies. MicroRNAs (miRs) can regulate multiple oncogenic pathways but require effective delivery systems due to their limited stability and delivery to tumors. Bone marrow-derived mesenchymal stem cells (BMSCs) exhibit intrinsic tumor-homing properties and therefore represent a promising biological source for tumor-directed drug delivery. Here, we developed BMSC membrane-polymersome hybrid nanovesicles (HNVs) that combine the tumor-homing potential of BMSC membranes with the structural stability of synthetic polymersomes for therapeutic miRNA delivery to HRNB.

Method: Cell membrane vesicles (CMVs) were isolated from BMSCs, and polymersomes were prepared using poly(ethylene glycol)-b-poly(lactic acid) (mPEG-b-PLA). HNVs were generated by extrusion at various CMV-to-polymersome ratios and characterized by dynamic light scattering (DLS), zeta potential, and fluorescence resonance energy transfer (FRET) analysis. Tumor-suppressive miR (miR-34a) was subsequently loaded into the optimized HNV formulation, and cellular uptake and therapeutic efficacy were evaluated in HRNB cells.

Results: HNVs were successfully formed across multiple CMV-to-polymersome compositions. Among the formulations tested, a 3:7 CMV-to-polymersome ratio showed favorable physicochemical stability and strong membrane-polymersome hybridization and was thus selected as the optimized formulation. Incorporation of BMSC membranes enhanced cellular uptake in HRNB cells compared with polymersomes alone, supporting the BMSC membrane-facilitated cellular uptake. Furthermore, delivery of the tumor-suppressive miR-34a-loaded HNVs significantly reduced HRNB cell viability, demonstrating functional miRNA delivery and therapeutic activity.

Conclusion: These results present a biomimetic HNV that integrates the tumor-homing potential of BMSC membranes with the physicochemical stability of polymersomes for efficient miR delivery to HRNB cells. Future studies will evaluate the tumor-targeting capability and therapeutic efficacy of miR-34a-loaded HNVs in HRNB models in vivo.

20-B TARGETING LYSOSOMAL VULNERABILITIES IN DRUG-TOLERANT PERSISTENT CELLS FOR MAINTENANCE THERAPY IN MUSCLE-INVASIVE BLADDER CANCER

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Muscle-invasive bladder cancer (MIBC) remains a highly aggressive disease with limited therapeutic options. Current standard-of-care treatment consists of cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy, yet only 35%–40% of patients achieve a pathologic complete response, leaving a substantial proportion with residual disease and a high risk of relapse. Drug-tolerant persistent (DTP) cells have emerged as a potential driver of treatment resistance by adopting a reversible, non-mutational dormant state that enables survival following cytotoxic therapy. DTP persistence is associated with enhanced autophagy-lysosome activity and an iron-dependent redox state, creating a therapeutic vulnerability that can be exploited through lysosomal disruption.

To target this vulnerability, we developed self-assembling nanoparticles based on novel bisaminoquinoline (BAQ) derivatives. BAQ13 forms tumor-selective nanoparticles that preferentially accumulate within the acidic lysosomal compartment. Following internalization, BAQ13 induces a proton-sponge effect that disrupts lysosomal acidification, promotes osmotic swelling, and ultimately triggers lysosomal membrane permeabilization (LMP). BAQ13 exhibited potent antitumor activity across multiple cancer models in vitro and in vivo and demonstrated a favorable therapeutic profile across xenograft models. Importantly, administration of BAQ13 as maintenance therapy following neoadjuvant cisplatin treatment suppressed tumor regrowth in an MIBC patient-derived xenograft (PDX) model compared with neoadjuvant cisplatin treatment only and untreated controls. Analysis of progression-free survival, overall survival, and persistent DTP populations further supports the role of lysosomal targeting in eliminating residual drug-tolerant tumor cells.

Collectively, these findings identify BAQ13 mediated lysosomal disruption as a potential maintenance strategy following neoadjuvant chemotherapy and provide a therapeutic approach for targeting residual DTP populations in MIBC.

21-A TARGETING EV-TOLERANT UROTHELIAL CANCER CELLS THROUGH SEQUENTIAL ENFORTUMAB VEDOTIN AND BAQ13 TREATMENT

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Advanced urothelial (bladder) cancers can carry a serious prognosis and have one of the highest recurrence rates among adult cancers. SW780 is a cell line isolated from a Grade 1 tumor and is a reliable model for non-muscle-invasive bladder cancer. Current therapies include the use of Enfortumab Vedotin (EV), an antibody drug conjugate (ADC) that works by attaching to Nectin-4, a protein that is readily expressed on the surface of urothelial cancer cells. This binding allows the drug to enter the cell and release a toxin, monomethyl auristatin E (MMAE), which prevents microtubule polymerization and leads to cell death. However, after a period of treatment, the cells can become drug-tolerant to the EV drug. To evaluate ways to combat this resistance, we established SW780 cells with EV therapy so they achieved a Drug Tolerant Persistent (DTP) state. Then, we treated the DTP state cells with our Small Molecule Inhibitor (SMH), BAQ13, an autophagy inhibitor that accumulates in the cell lysosome. As a result, we found that BAQ13 has high antitumor effects against the parental SW780 cell line as well as the DTP state cell line, as it increased both lysosome disruption and autophagy disruption, which led to cell death. BAQ13 is a promising candidate to treat DTP state SW780 cells as it has demonstrated strong in vivo anti-tumor activity (about 30x stronger than hydroxychloroquine). This suggests an alternative and possibly more successful route for treating urothelial cancer through combination therapy of two drugs, EV and BAQ13, compared to the current sole use of EV. Next, we plan to observe transmission electron microscopy (TEM) imaging to determine the extent of lysosome disruption.

22-B INCIDENCE, PREDICTORS, AND TREATMENT IMPACT OF SEVERE THROMBOCYTOPENIA DURING CONCURRENT CHEMORADIATION FOR GLIOBLASTOMA

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Background: Temozolomide (TMZ) combined with radiation therapy (RT) is the standard-of-care for newly diagnosed glioblastoma (GBM), with both concurrent and adjuvant TMZ conferring a survival benefit. Although thrombocytopenia is a recognized toxicity of TMZ, its impact on treatment continuity and adjuvant therapy delivery remains incompletely characterized.

Objective: To determine incidence, clinical predictors, and treatment impact of grade 3–4 thrombocytopenia during concurrent RT/TMZ in GBM patients.

Methods: In this retrospective single-institution cohort study, fourteen patients who developed grade 3–4 thrombocytopenia during concurrent RT/TMZ were identified in an institutional GBM cohort. Descriptive statistics were used to describe baseline characteristics. Platelet nadir, time to nadir, treatment interruptions, transfusion requirements, and receipt of adjuvant TMZ were reported.

Results: Among 197 patients with newly diagnosed GBM treated with concurrent RT/TMZ since August 2020, 14 patients (7.1%) developed grade 3–4 thrombocytopenia; 57% female, median age of 72.3 years, and 7% MGMT methylated. Median baseline platelet count was $225 \times 10^3/\mu\text{L}$ with platelet nadir of $25 \times 10^3/\mu\text{L}$, occurring at a median of 46 days from treatment initiation. Median TMZ exposure during the concurrent phase was 32 days (range 21–45). TMZ was discontinued in 9 of 14 patients (64%) during concurrent RT/TMZ. Platelet transfusion was required in 9 of 14 patients (64%). Only 4 of 14 patients (29%) went on to receive adjuvant TMZ. Among patients who permanently discontinued TMZ during chemoradiation, 7 of 9 (78%) did not receive any adjuvant TMZ.

Conclusions: Severe thrombocytopenia during concurrent chemoradiation frequently leads to permanent TMZ discontinuation and precludes delivery of adjuvant TMZ, potentially compromising overall treatment efficacy. Most patients who permanently discontinue TMZ during the concurrent phase fail to receive adjuvant TMZ, forfeiting potential additional survival benefit. These findings highlight the need for proactive hematologic monitoring and risk-adapted strategies to preserve treatment continuity in this population.

23-A IGF1 BINDING TO INTEGRIN $\alpha\text{V}\beta 3$ INDUCES DIRECT G α 13 BINDING TO IGF1R KINASE

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IGF1 plays a critical role in cell proliferation and survival. IGF1 and IGF1 receptor (IGF1R) are over expressed in cancer and are major therapeutic targets. Previous studies show that IGF1 binds to integrin $\alpha\text{V}\beta 3$ and induces $\alpha\text{V}\beta 3$ -IGF1-IGF1R ternary complex formation. However, how IGF1 binding to $\alpha\text{V}\beta 3$ leads to IGF1R activation is unclear. Previous studies showed that G α 13, a guanine nucleotide-binding protein of the G12 class of G α proteins, binds to the integrin $\beta 3$ tail through the EEE motif upon fibrinogen binding to integrin $\alpha\text{IIb}\beta 3$ and induces RhoA activation. We discovered that the EEE/AAA mutation of the $\beta 3$ tail inhibited IGF1-induced cell survival, suggesting that G α 13 binding to the $\beta 3$ tail is required for IGF1 signaling. Since RhoA activation may not be directly involved in IGF1R activation, we studied if G α 13 binds to molecules other than RhoA. Since G α 13 binds to several cytoplasmic tyrosine kinases, we studied if G α 13 binds to the IGF1R kinase by a docking simulation. The simulation predicted that G α 13 binds to the IGF1R kinase through a new binding site. Mutating the predicted G α 13 binding site in the IGF1R kinase (residues 1020–1022) or the predicted IGF1R kinase binding site in G α 13 (residues 260–279) inhibited G α 13 binding to the IGF1R kinase, which is consistent with the docking model. Notably, the G α 13(260–279A) mutant inhibited IGF1-induced cell survival. We propose that IGF1 binding to $\alpha\text{V}\beta 3$ induces G α 13 binding to the $\beta 3$ tail and subsequent G α 13 binding to the IGF1R kinase, leading to IGF1R activation. Interestingly, G α 13(260–279A) mutation inhibited cell survival due to a constitutively active G α 13(Q226L) mutant. We propose that G α 13(Q226L) induces its effect by binding to the IGF1R kinase. We propose that the G α 13 binding site of the IGF1R kinase or the IGF1R binding site in G α 13 may be a novel therapeutic target.

24-B ULTRASMALL PLZ4-DM1 NANOCONJUGATES FOR TARGETED BLADDER CANCER THERAPY

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Bladder cancer (BdCa) is one of the most prevalent urologic malignancies, with significant morbidity and mortality. Current standard-of-care for non-muscle invasive bladder cancer (NMIBC) relies on intravesical BCG immunotherapy and transurethral resection, while advanced muscle-invasive and metastatic disease is treated with highly toxic platinum-based chemotherapy or antibody-drug conjugates (ADCs). Two FDA-approved ADCs for bladder cancer: Enfortumab vedotin and Sacituzumab govitecan demonstrate clinical efficacy but carry dose-limiting toxicities including neutropenia, peripheral neuropathy, and hepatotoxicity, driven in part by their Fc-receptor binding domains and large particle sizes (~ 10 nm) that limit tumor penetration. There is a critical unmet need for more efficacious, less toxic, and easily scalable therapeutic platforms for both superficial and advanced BdCa.

We propose a nanoplateform consisting of activate target ligand PLZ4, previously developed in the Lam lab via one-beads-one-compound (OBOC) combinatorial library method is a disulfide cyclic peptide, cQDGRMGFC, which targets $\alpha\text{V}\beta 3$ integrin found to be overexpressed in BdCa. The toxin DM1 will be covalently linked to the peptide conjugate via a cleavable linkage (e.g. disulfide cleavable by glutathione) or a non-cleavable MCC-thioether linkage used in Ado-Trastuzumab, with DM1 released inside lysosomes. We hypothesize that an ultrasmall (2–5 nm) PLZ4-targeting DM1 nanoconjugate (PLZ4-nanoDM1) will demonstrate efficacy at least comparable to existing ADCs against BdCa, while exhibiting a significantly improved safety profile.

25-A EXPLORING THE IMPACT OF CD155-TIGIT AXIS IN NK CELL IMMUNOTHERAPY FOR BONE AND SOFT TISSUE SARCOMA

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Background: TIGIT (T cell immunoreceptor with Ig and ITIM domains) has emerged as a key exhaustion marker of intratumoral natural killer (NK) cells, but clinical trials results with TIGIT blockade have been largely negative. Recent data suggest that a subset of TIGIT-expressing NK cells show increased functionality. We hypothesized that there are functional differences between peripheral and intratumoral TIGIT-expressing NK cells in sarcoma patients and preclinical sarcoma models, which undermine the efficacy of systemic TIGIT blockade. We sought to investigate differences in TIGIT+ NK cells using systemic versus intratumoral TIGIT-blocking strategies.

Methods: Peripheral and intratumoral NK cells were analyzed from human patients and mice with osteosarcoma (OSA) and soft tissue sarcoma (STS). NK phenotype and function were evaluated using flow cytometry, immunohistochemistry, live-cell imaging, and RNA sequencing. Mouse antimouse-IgG1 TIGIT blockade was delivered systemically or intratumorally in flank models of OSA (K7M2) and STS (MCA-205). Clinical and genomic data were evaluated using Caris CODEai. TIGIT ligand CD155 expression was evaluated on myeloid and tumor cells as a marker of TIGIT function.

Results: Using multiple readouts, TIGIT+ NK cells from the spleen of tumor-bearing mice or peripheral blood of STS and OSA patients showed increased functionality compared with TIGIT- NK, while TIGIT+ NK cells from the sarcoma tumor microenvironment (TME) of mice and humans were dysfunctional, with upregulated senescence and inhibitory gene pathways. Systemic TIGIT blockade reinvigorated intratumoral NK cell function but inhibited peripheral NK cells, while intratumoral administration of TIGIT blockade significantly delayed tumor growth and prolonged survival with partial reversal of NK dysfunction in the TME. Clinical and genomic data demonstrated that more NK cell infiltration in human STS was prognostic of improved overall survival only when intratumoral CD155 expression was low, indicating that elevated CD155 expression is correlated with greater NK cell dysfunction.

Conclusions: We identified a cross-species role of location-dependent TIGIT expression, where peripheral TIGIT+ NK cells showed evidence of enhanced functionality, while intratumoral TIGIT+ NK cells were dysfunctional. These differences impacted antitumor effects of TIGIT blockade, suggesting that intratumoral delivery of TIGIT blockade may be a novel translational strategy in high-risk bone and soft tissue sarcomas.

26-B NOVEL SPLEEN-TROPIC BISAMINOQUINOLINE DERIVATIVES FOR DUAL CHEMO- AND MRNA-BASED CANCER THERAPY

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The development of versatile nanomedicine for oncology requires overcoming limitations such as off-target liver accumulation and limited therapeutic functionality. Here, we evaluated a series of bisaminoquinoline derivatives as multifunctional ionizable lipids for mRNA delivery and cancer-cell killing. Two lead compounds, YXL-474-3 and YXL-527-2, demonstrated efficient mRNA transfection in MIA PaCa-2 (pancreatic) and OSC3 (head and neck) cancer cell lines while exhibiting intrinsic cytotoxic activity, with IC50 values of approximately 100 μ M and 25 μ M, respectively. Importantly, both compounds exhibited mRNA delivery and cancer-cell-killing activities. LNPs were self-assembled using either microfluidic or simple mixing methods with helper lipids, including cholesterol, DOPE, and DMG-PEG2000. Using eGFP mRNA as a reporter, both lead LNP formulations demonstrated superior in vitro transfection compared with D-Lin-MC3-DMA LNPs in MIA PaCa-2 and OSC3 cells. Optimized formulations generated stable nanoparticles ranging from 120 to 200 nm with mRNA encapsulation efficiencies exceeding 80%, which were further improved by varying the concentrations of the LNP components during formulation optimization. In vivo biodistribution studies using luciferase mRNA showed that both YXL-474-3 and YXL527-2 LNPs exhibited spleen tropism, demonstrating preferential extrahepatic accumulation. Overall, these findings establish bisaminoquinoline lipids as multifunctional LNP components that combine enhanced mRNA delivery, spleen tropism, and intrinsic cancer-cell killing, providing a promising foundation for targeted cancer nanomedicine.

27-A EFFECTS OF A BACTERIAL 4-THIOURIDINE MODIFICATION ON THE ANTI-CANCER ACTIVITY OF BIOENGINEERED LET-7E-5P IN NSCLC CELLS

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To better mimic the properties of endogenous miRNA molecules, our lab has established a novel human tRNA-fused hsa-pre-miR-34a carrier-based RNA bioengineering platform to offer biologic miRNAs (BioRNAs) in consistent, high-yield, and large-scale production through in vivo bacterial fermentation. Screening of tumor-suppressive let-7-5p isoforms revealed BioRNAGly/let-7e-5p as the leading suppressor of human non-small cell lung cancer (NSCLC) cell viability, demonstrating strong therapeutic potential for NSCLC. While highly conserved posttranscriptional modifications (dihydrouridine in the D-loop as well as 5-methyluridine and pseudouridine in the T-loop) were observed together with the absence of modifications on the pre-miR carrier and payload miRNA, liquid chromatography-tandem mass spectrometry (LC-MS/MS) and nanopore direct RNA sequencing studies revealed a bacteria-specific 4-thiouridine (s4U) posttranscriptional modification at position 8 of the tRNA segment. To evaluate the possible effects of s4U on the mature miRNA release and anti-cancer efficacy of BioRNAGly/let-7e-5p, we re-innovated our BioRNA technology to bypass s4U modification through either base substitution at position 8 or expression in an E. coli strain deficient in s4U synthesis. These two distinct strategies successfully abrogated the s4U modification on BioRNAGly/let-7e-5p, without compromising the yield of production or changing the profiles of highly conserved modifications. Surprisingly, comprehensive comparative analyses showed that the distal s4U modification minimally affected the release of let-7e-5p from the BioRNA and its efficacy to repress multiple targeted oncogenes in NSCLC cells. These insights establish a foundation for developing BioRNAGly/let-7e-5p as a potential therapeutic agent against NSCLC.

28-B PRODUCTION AND USE OF RECOMBINANT MIRNAS TO DISSECT THE INTRINSIC DIFFERENCES IN MIRNA BIOGENESIS AND REGULATION OF DRUG METABOLISM IN HEPATOCELLULAR CARCINOMA CELLS

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Variability in the expression of drug-metabolizing enzymes can significantly drive inter-individual differences in chemotherapeutic exposure, efficacy, and toxicity. UDP-glucuronosyltransferase 1A1 (UGT1A1) is a critical clearance enzyme responsible for inactivating key oncological agents (e.g., SN-38, 4-hydroxy-tamoxifen, and endoxifen), and its dysregulation is strongly implicated in cancer chemoresistance or drug-induced toxicities. While microRNAs (miRNAs) are known to be post-transcriptional regulators of metabolic genes, this study aimed to employ our novel recombinant RNA technology to design, express, and purify recombinant human miR-491-5p, miR-491-3p, and pre-miR-491 molecules (BioRNAs) to investigate their biogenesis and functional capacity to modulate UGT1A1-mediated drug metabolism in hepatocellular carcinoma cells (Hep3B and HepG2). To this end, we have successfully designed, cloned, expressed, and purified two sets (human tRNAGly or tRNA^{Leu} scaffolds) of recombinant pre-miR-491, miR-491-5p, and -3p molecules (BioRNAs) with high yields ($\geq 30\%$ of total RNA) and high purities ($\geq 97\%$ by HPLC). Our RT-qPCR studies revealed that the BioRNA/pre-miR-491 was predominantly processed into the 5p strand in Hep3B and HepG2 cells, and the bioengineered BioRNA/miR-491-5p and -3p were selectively processed into 5p and 3p strands. Immunoblotting and immunofluorescence confocal imaging demonstrated that BioRNA/miR-491-3p effectively downregulated UGT1A1 protein levels, while BioRNA/pre-miR-491 and miR-491-5p had no effects in Hep3B and HepG2 cells. Furthermore, a reduction of up to 45% in UGT1A1-mediated xenobiotic metabolism by miR-491-3p was further revealed using selective index reactions, NHPN glucuronidation, and estradiol-3-glucuronidation. Together, these findings show that recombinant BioRNAs are powerful tools for studying miRNA-controlled gene regulations, which offer insights into the importance of post-transcriptional gene regulation mechanisms in cancer cells.

29-A A NEW CLINICAL ENTITY: RETROSPECTIVE CASE STUDY OF IMMUNE CHECKPOINT INHIBITOR INDUCED MYASTHENIA GRAVIS

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Background: Immune checkpoint inhibitors (ICI) represent a breakthrough in cancer treatment, but immune related adverse events (irAEs), including neuromuscular complications, have been increasing with the increased ICI usage. ICI induced myasthenia gravis (iMG) appears to have a unique clinical presentation, different from spontaneous MG. In this case series study, we aim to characterize the clinical features of iMG to help achieve timely management of this disorder.

Methods: We have retrospectively analyzed twelve cases with the clinical diagnosis of iMG presenting from Jan 2020 to Dec 2025 in the Sacramento metropolitan area.

Results: History and physical examination showed that all cases of iMG had fatigable weakness. The common symptoms were similar to spontaneous MG. Only one case had ocular myasthenia gravis, the remaining eleven had generalized MG (Myasthenia Gravis Foundation of America Class III to IV). The patients' mean age was 72.6 years, nine of twelve were men. The most common cancer was renal cell carcinoma (5/12), followed by bladder cancer (2/12), melanoma (2/12), squamous cell carcinoma (2/12). The most used ICI was Pembrolizumab (5/12), followed by Nivolumab (4/12). Four cases underwent dual ICIs or ICI combined with chemotherapy. The time from initiation of ICI treatment to symptom onset ranged from 3 days to 6 weeks. Two had positive acetylcholine receptor antibodies. Other autoantibodies were detected: one had striated muscle antibody, one had ANA as well as positive SSA, and one had GAD antibody. Ten iMG cases presented with overlap syndromes: five had myositis and myocarditis, four had myositis, one had myocarditis and hepatitis. Two received muscle biopsy that demonstrated multifocal muscle fiber necrosis in clusters. High-dose steroids, intravenous immunoglobulin, and pyridostigmine were the most commonly used treatments. Two cases received Abatacept and Roxolitinib with moderate improvements. Despite some clinical improvement to the above treatments, the mortality for iMG was 50%.

Conclusion: This case series study indicates that: 1) iMG usually presents with more severe symptoms than spontaneous MG; 2) overlap syndromes are common in iMG, 4) along with increased mortality. Therefore, we propose that iMG is a new clinical entity with unique features that may have a different pathophysiology.

30-B A NOVEL ROR γ INHIBITOR SUPPRESSES PANCREATIC CANCER BY DRIVING NCOA4-MEDIATED FERRITINOPHAGY VIA THE NOTCH1/HES1 AXIS

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Pancreatic cancer remains a highly lethal malignancy with limited therapeutic options. Here, we identify retinoic acid receptor-related orphan receptor gamma (ROR γ) as a key prognostic biomarker and therapeutic target in pancreatic cancer. Through structural optimization of known ROR γ antagonists, we synthesized a novel series of 5-phenylindole-amide derivatives and identified YXL306 as a potent, subtype-selective ROR γ inhibitor. Rationally designed as an ester prodrug to facilitate intracellular accumulation via ion trapping, YXL306 exhibits superior antiproliferative, anti-invasive, and pro-apoptotic activities compared to reference inhibitors. Integrated RNA-seq and biophysical analyses revealed that ROR γ directly transactivates the Notch signaling pathway, in which HES1 acts as a downstream transcriptional repressor of NCOA4. Inhibition of ROR γ relieves HES1-mediated repression, inducing NCOA4-dependent ferritinophagy, intracellular Fe²⁺ accumulation, mitochondrial dysfunction, and lipid peroxidation-driven ferroptosis. In vivo, YXL306 administered either intraperitoneally or orally markedly suppressed primary tumor growth, blocked pulmonary metastasis, and significantly prolonged overall survival in both cell line-derived (CDX) and patient-derived xenograft (PDX) mouse models without inducing systemic toxicity. Overall, our findings uncover a previously unrecognized ROR γ -Notch-NCOA4 regulatory axis and highlight YXL306 as a promising therapeutic lead for pancreatic cancer.

31-A A VISION-GUIDED, HIGH-THROUGHPUT RAMAN PROBING ROBOT ENABLING DEEP LEARNING FOR POINT-OF-CARE CANCER SCREENING FROM BLOOD PLASMA

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Head and neck squamous cell carcinoma (HNSCC) accounts for roughly 60,000 new cases and 12,000 deaths annually in the U.S. Five-year survival exceeds 90% for early-stage disease but falls below 50% once advanced, yet no FDA-approved screening test exists. Tissue biopsy, the diagnostic standard, is invasive, slow, and confined to specialized centers, motivating a minimally invasive test suited to point-of-care screening. Raman spectroscopy of a microliter blood-plasma drop is well matched to this setting. It is rapid, label-free, requires minimal sample preparation, and captures a broad metabolic signature rather than a single biomarker. Despite this promise, Raman scattering is inherently weak and confounded by fluorescence, noise, and patient covariates, and classification models trained on small, inconsistent datasets fail to generalize across the patient populations screening would require.

This work addresses the data bottleneck with a high-throughput, vision-guided Raman platform that generates the large, standardized spectral datasets such models require. We converted a low-cost 3D-printer stage into an automated Raman probing robot in which computer vision drives autonomy and data quality, demonstrating that acquisition can run on accessible hardware. We built the imaging system and developed Python control software synchronizing cameras, lasers, and motion stages, and implemented deep-learning segmentation for sample localization and real-time quality assurance. This feedback loop locates, focuses on, and scans 192 dried plasma spots unattended within eight hours, increasing throughput 20-fold over manual acquisition. Using this platform, we show a prediction model trained on a standardized spectral dataset from a 300-patient cohort, a step toward a low-cost, generalizable point-of-care blood test for early HNSCC screening.

32-B DYNAMIC [¹⁸F]FAPI-74 PET AS A NON-INVASIVE BIOMARKER OF LIVER FIBROSIS SEVERITY IN MASLD

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Purpose/Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a rapidly growing driver of hepatocellular carcinoma (HCC), one of the leading causes of cancer-related death worldwide. As with other chronic liver diseases, HCC risk in MASLD rises progressively with the degree of hepatic fibrosis, making accurate fibrosis assessment essential for identifying patients at greatest oncologic risk. However, liver biopsy, the current reference standard for fibrosis staging, is invasive and poorly suited to repeated assessment, and existing non-invasive tests only indirectly estimate fibrosis burden and lack sensitivity to active, ongoing fibrogenesis. Fibroblast activation protein (FAP) is selectively expressed on activated hepatic stellate cells during fibrogenesis, providing a molecular target that could enable direct, quantitative imaging of fibrogenic activity rather than its downstream structural consequences. We hypothesized that dynamic total-body PET using the FAP inhibitor [¹⁸F]FAPI-74 could non-invasively quantify hepatic fibrogenic activity and stage fibrosis severity in MASLD. This pilot study evaluated that approach.

Methods: Ten participants were enrolled, including three healthy controls and seven MASLD patients biopsy-staged by NASH-CRN criteria (F1/2=3; F3/4=4). All participants received 215–236 MBq [¹⁸F]FAPI-74 followed by 60-minute dynamic total-body PET/CT. Volumes of interest (VOIs) were placed in eight Couinaud liver segments and the descending aorta to derive the arterial input function. SUVmean, SUVR, and net influx rate (Ki), estimated via dual-input two-tissue compartment modeling, were derived and correlated with histologic fibrosis stage using the Kruskal–Wallis test and Spearman's rank correlation.

Results: Hepatic [¹⁸F]FAPI-74 uptake increased progressively with fibrosis severity across all PET-derived metrics. Median SUVmean was 3.35, 4.12, and 4.73 in healthy controls, F1/2, and F3/4, respectively; corresponding SUVR values were 0.48, 0.54, and 0.66; and Ki values were 14.18, 22.02, and 32.85 (×10⁻³ mL/min/cm³). Both SUVR (ρ=0.95, p<0.001) and Ki (ρ=0.84, p<0.002) showed strong correlation with histologic fibrosis stage, outperforming SUVmean alone.

Conclusion: Dynamic [¹⁸F]FAPI-74 PET quantifies hepatic fibroblast activation, correlating strongly with fibrosis stage and offering a promising biomarker for monitoring MASLD progression and HCC risk.

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33-A IN VIVO FLUORESCENCE LIFETIME IMAGING OF COLORECTAL POLYPS

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Colorectal cancer (CRC) ranks third in cancer diagnoses worldwide and second in cancer-related deaths, with an increasing incidence rate in young adults under 50. Screening and surveillance tools aid in the early detection of CRC. However, current endoscopic procedures, which identify lesions by shape and surface pattern, lack biochemical specificity that distinguishes benign, precancerous, and malignant colorectal polyps.

Our study uses label-free fluorescence lifetime imaging (FLIm) to phenotype colonic polyps during colonoscopy, targeting the biochemical signatures associated with polyp progression. Studies have shown that colorectal polyps exhibit measurably altered structural and metabolic activity compared to normal mucosa. Metabolic reprogramming favoring aerobic glycolysis in carcinoma has been detected as

early as the adenomatous stage, altering the balance between NAD(P)H and FAD before malignant transformation. Structural alterations occur as polyps transition from benign to precancerous, leading to an increase in collagen types I, VI, XIV. Our imaging system utilizes pulse-sampling FLIM to collect measurements from the patients' colonic mucosa using a 355 nm pulsed laser and four pre-filtered avalanche photodiode detectors (APDs) at 390/40 nm, 470/28 nm, 540/50 nm, and 630/50 nm spectral bands. Lifetime changes in structural proteins are primarily captured in the 390/40 nm channel, while changes in metabolic cofactors NAD(P)H and FAD are captured in the 470/28 nm and the 540/50 nm channels, respectively.

We have collected 8 in vivo autofluorescence measurements of polyps from 8 patients undergoing colonoscopy, pairing each measurement with its adjacent normal (deemed healthy) mucosa as reference. An initial preliminary study from 18 patients with 134 FLIM measurements suggests significant differences (Mann-Whitney U test) across the 390 nm, 470 nm, and 540 nm spectral channels. These findings suggest a potential role of FLIM in augmenting CRC screening and surveillance, particularly for early-stage lesions.

34-B FEASIBILITY OF CHEMICAL EXCHANGE SATURATION TRANSFER (CEST) MRI FOR ASSESSING MOLECULAR BIOMARKERS AT TMJ CONDYLAR BONE MARROW

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Background: Malignant tumors in the temporomandibular joint (TMJ), such as chondrosarcoma and osteosarcoma, are rare and frequently exhibit the same symptoms as TMJ dysfunction with pain and swelling, which can lead to misdiagnosis or delayed diagnosis. CBCT and MRI are used for diagnosis and to assess the extent and involvement of bone tumours. Molecular CEST MR imaging can capture certain biomolecules, such as glycosaminoglycans (GAGs). A study of rat chondrosarcoma model reported elevated gagCEST signal, suggesting its potential as a biomarker for bone tumours. In this preliminary study, we acquired TMJ CEST MRI and demonstrated measurable CEST effects at 3T.

Objectives: To assess the feasibility of CEST MRI for characterizing molecular contribution at TMJ condylar bone marrow in a healthy volunteer.

Methods: A healthy volunteer underwent a standard closed-mouthed TMJ imaging protocols, such as proton density (PD) and fast spin echo-based CEST on a 3T GE scanner. CEST MRI was acquired using two RF saturation schemes: a low-power pulse for B0 correction and a CEST pulse. CEST frequencies were sampled from -7 to +7 ppm. Using in-house software, CEST images were registered to a PD scan. Offset images were normalized using a non-saturated reference scan and corrected for B0 inhomogeneity. Contrast maps were generated using relaxation-compensated inverse magnetization transfer ratio (MTRRex) and a multi-pool Lorentzian (MPL) fit. Seven pools were included in the analysis: water, hydroxyl, amide, NOE, amine, fat and MT. An ROI was placed within the mandibular condylar marrow. CEST effects were isolated and compared.

Results: CEST effects at the condyle are distinguishable with MPL fit ($R^2 > 0.95$) and MTRRex. Distinct water, NOE and fat signals are observed on MPL and MTRRex metrics (b-c). Direct water saturation was reduced using MTRRex (c), enabling characterization of exchange-related contrast. The resulting contrast maps revealed heterogeneous molecular distributions within the ROI (d-q).

Conclusion: CEST MRI is feasible for characterizing molecular contribution at the mandibular condylar bone marrow. The baseline could be established to provide a reference for future studies of pathological TMJ changes. Challenges remain in non-standard acquisition to obtain unbiased CEST effects and in incorporating B1 inhomogeneity and motion corrections.

35-A CELLULAR MORPHOMETRIC BIOMARKERS FROM ROUTINE PATHOLOGY PREDICT EARLY METASTATIC RISK IN CANINE OSTEOSARCOMA

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Canine osteosarcoma is an aggressive malignancy in which occult metastatic disease is common despite local control and adjuvant chemotherapy. In collaboration with Dr. Hang Chang, who developed the Cellular Morphometric Biomarker (CMB) framework, we applied this artificial intelligence-based approach to routine hematoxylin and eosin (HandE) pathology slides to extract and analyze 256 quantitative morphometric features using prespecified morphologic rules, and quantified using predefined single-cell and spatial features. Our goal was to determine whether pretreatment tumor morphology could identify dogs at increased risk of early metastatic failure and whether these signals remained informative across spatially distinct tumor regions.

Across two comparative oncology cohorts of canine appendicular osteosarcoma, a naturally occurring model that shares important clinical and biological features with human osteosarcoma, we developed and locked a compact three-feature CMB score. The same fixed score reproducibly identified dogs at increased risk of early metastatic progression in both cohorts, with a median AUC of 0.690 and a stepwise increase in risk as additional adverse features were present. The score also predicted shorter disease-free interval and overall survival. Regional analyses suggested a hotspot-like pattern, in which a single high-risk tumor region conferred nearly the same early metastatic risk as tumors with multiple high-risk regions, consistent with a focal aggressive compartment driving clinical failure. The score remained independently prognostic after adjustment for established clinical factors, including alkaline phosphatase status and tumor location. RNA sequencing further linked the high-risk morphology to proliferative, DNA-repair, and mitochondrial programs, while poor outcome was also associated with reduced interferon signaling and antigen-presentation activity.

These findings support CMBs derived from routine HandE slides as a compact, biologically anchored tool for stratifying early metastatic risk in canine osteosarcoma. Our next step is to pair CMB profiling with matched functional 3D-bioprinted canine tumoroids to determine whether morphologic risk states can also inform therapeutic vulnerabilities. Ultimately, we hope to test whether these morphologic states can translate to human osteosarcoma for cross-species risk stratification and therapeutic discovery.

36-B [68Ga]Ga DOTA-5G PET/CT IMAGING IN PATIENTS DIAGNOSED WITH METASTATIC/ADVANCED INVASIVE LOBULAR BREAST CANCER

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This is a prospective study using [68Ga]Ga DOTA-5G PET/CT imaging in patients diagnosed with metastatic/advanced invasive lobular breast cancer (LBC). LBC accounts for 10-15% of all breast cancers. LBC is difficult to detect using current imaging approaches such as mammography, ultrasound, MRI, and 18F-FDG-PET/CT; Therefore, patients with advanced invasive LBC may have more extensive disease than detected using current imaging modalities. There remains a critical unmet need for minimally invasive approaches for both the earlier detection as well as the treatment of LBC. To address this unmet need we are proposing a molecularly targeted approach via the integrin $\alpha v \beta 6$ and [68Ga]Ga DOTA-5G PET/CT imaging. [68Ga]Ga DOTA-5G is an $\alpha v \beta 6$ -integrin-targeted peptide, radiolabeled with gallium-68, that is being developed as a diagnostic imaging agent (NCT04665947, NCT06228482, NCT06389123). We hypothesize that a) [68Ga]Ga DOTA-5G detects lesions in patients with LBC, b) [68Ga]Ga DOTA-5G is safe and well tolerated, and c) [68Ga]Ga DOTA-5G is more sensitive than 18F-FDG PET.

Patients diagnosed with LBC are being enrolled to study. Patients undergo [68Ga]Ga DOTA-5G PET/CT imaging within 6 weeks of routine standard-of-care 18F-FDG-PET imaging. At the time of the scan, up to 185 MBq of [68Ga]Ga DOTA-5G is injected IV. Patients then undergo scanning from the apex of the skull to the proximal thigh at approximately 1 hour and 2 hours post injection. Blood samples are obtained at serial time points for time-activity-curve calculations, vitals, blood samples, and EKG are also checked at 1 and 7 days after injection for full chemistry, hematology, and liver function tests.

To date three patients have completed the study. [68Ga]Ga DOTA-5G PET was safe and well tolerated. [68Ga]Ga DOTA-5G PET/CT imaging was able to detect lesions in bone and liver not previously detected with 18F-FDG-PET or 18F-FES-PET. Preliminary data suggest [68Ga]Ga DOTA-5G PET/CT is more sensitive than 18F-FDG-PET/CT and warrants further investigation. If successful, this study could be immediately translated to the clinic with the deployment of our molecularly targeted radiopharmaceutical therapeutic, [177Lu]Lu DOTA-ABM-5G, for the treatment of metastatic LBC.

37-A INTEGRATING HARMONIZED MRI/CT WITH PATHOLOGY-DERIVED GROUND TRUTH FOR MACHINE LEARNING IN SOFT TISSUE TUMORS

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Background: Soft tissue tumors (STTs) comprise a rare and heterogeneous group of neoplasms with substantial variation in imaging appearance, histology, and biological behavior. Development of robust machine-learning models for STT characterization requires standardized imaging linked to reliable pathology-derived ground truth. We developed a harmonized MRI/CT dataset and initiated systematic extraction of pathology features relevant to future imaging-based phenotype and grade prediction.

Methods: Diagnostic MRI and CT examinations were processed using a reproducible Python/SimpleITK pipeline incorporating DICOM-to-NIfTI conversion, orientation standardization, modality-specific intensity preprocessing, spatial resampling, artifact exclusion, and automated quality-control logging. CT and MRI volumes were resampled to 1.0-mm and 1.5-mm isotropic spacing, respectively. Pathology reports from cases categorized within the current malignant dataset were manually reviewed for histologic phenotype, explicitly documented FNCLCC grade, mitotic rate, and tumor necrosis. FNCLCC grade was recorded only when explicitly stated in the pathology report and was not inferred from individual histologic features.

Results: To date, 307 scans have been harmonized, including 172 CT and 135 MRI examinations, with 100% processing QC success. Pathology review included 74 reports spanning nine STT phenotypes. FNCLCC grade was explicitly documented in 15/74 reports (20.3%), mitotic rate in 19/74 (25.7%), and necrosis in 16/74 (21.6%). Documentation varied substantially by phenotype. Among six pleomorphic liposarcoma reports, FNCLCC grade, mitotic rate, and necrosis were documented in 5/6, 6/6, and 6/6, respectively. Conversely, among 27 fibrosarcoma reports, these features were documented in only 2/27, 3/27, and 3/27. Among 11 epithelioid sarcoma reports, no explicit FNCLCC grade was identified despite documentation of mitotic rate in four and necrosis in three.

Conclusions: Integration of harmonized imaging with structured pathology review provides a scalable framework for STT machine learning while revealing substantial phenotype-dependent variability in pathology ground-truth availability. Explicit identification of missing grading labels is essential for defining reliable training cohorts and developing future radiomics and deep-learning models for noninvasive STT characterization and grade prediction.

38-B INVESTIGATION OF CIRCULATING EXTRACELLULAR VESICLES AS CANDIDATE BIOMARKERS FOR CANINE GLIOMAS

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Background: Glioblastoma is an aggressive and diagnostically challenging primary brain tumor in dogs, as diagnosis and monitoring often rely on advanced imaging alone. Currently, there is no molecularly informed diagnostic tool available for canine glioma management.

Hypothesis: I hypothesize that canine glioblastoma produces a reproducible EV signature that can be measured by single-particle flow cytometry, and that this signature is stronger and more tumor-specific in CSF than in serum.

Objectives:

1) Define candidate EV surface and signatures of canine glioblastoma using single-particle flow cytometry.

2) Compare the diagnostic strength of EV signatures in CSF versus serum from canine glioma patients.

Methods: J3T and G06 canine glioma EVs were isolated via ultracentrifugation (UC). Following antibody staining protocols, CD9, CD44, and IL-13R α 2 EV surface markers were measured using single-particle flow cytometry. CD9 is a tetraspanin protein used to identify lipid-bound EVs. CD44 is a cell surface glycoprotein involved in glioma progression and spread. IL-13R α 2 is an immune modulator that is highly associated with glioma and is absent in healthy brain tissue. Paired serum and cerebrospinal fluid (CSF) samples were acquired from the neurology service at the UC Davis School of Veterinary Medicine.

Results: In this study, a single-particle flow cytometry panel for the interrogation of canine gliomas was successfully designed. A high volume of canine-derived EVs was isolated via bioreactor. CD9, CD44, and IL-13R α 2 antibodies were validated for use in canine EVs for single-particle flow cytometry. CD9 and CD44 antibodies showed positivity among canine glioma cells, while troubleshooting is needed to assess IL-13R α 2 antibodies due to possible aggregation. Notably, J3T cells displayed the highest levels of CD44 expression, followed by G06 and HEK. This trend reflects cell line biology, as J3T cells model a highly aggressive form of glioma, with G06 being less robust.

Conclusion: Results from patient serum and CSF samples are pending. These experiments validate our antibodies against proteins of interest on J3T and G06 canine glioma-derived EVs. Future directions include exploring other potential biomarkers, including but not limited to surface glycans like sialic acids. Our methods development acts as a catalyst for downstream EV characterization experiments and biomarker discovery.

39-A Y-90 RADIOEMBOLIZATION DISTRIBUTION PREDICTION FROM PRETREATMENT IMAGING USING 3D CGANS

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Introduction: Yttrium-90 (Y-90) radioembolization is a targeted liver cancer treatment in which radioactive microspheres are injected into the hepatic artery. Current treatment planning involves computed tomography (CT) based vascular inspection; the dose and injection site are selected qualitatively, targeting a liver segment or lobe. There is a need to develop more efficient treatment planning methods as the quality of treatment improves with more personalized planning. The goal of this study is to demonstrate the feasibility of using generative artificial intelligence to generate personalized Y-90 treatment plans based on each patient's vascular anatomy obtained from pre-treatment CT scans.

Materials and Methods: A 3-D conditional Generative Adversarial Network (cGAN) was designed to generate realistic Y-90 distributions, resembling post-treatment PET. The generator uses a U-Net style encoder-decoder with 5 downsampling and 5 upsampling layers. The discriminator has four convolutional layers. Pre-treatment CECT images from a cohort of 30 subjects were used to create the 4008 pair training dataset in this study. PET-like distributions were created by taking the difference between the base CECT and the arterial phase images. The network was trained for 25000 epochs. Generated distributions were compared with the reference using visual assessment, mean absolute error, dose-volume histograms (DVH), and structural similarity index measure (SSIM).

Results and Discussion: The cGAN generated realistic output with strong spatial agreement to the reference images. The mean DVH difference across tumor volumes was 8.37% with best- and worst-case mean differences of 2.31% and 17.39%, respectively. Mean SSIM across all patients in the test set was 0.97.

Conclusions: This study demonstrates the feasibility of using generative adversarial networks to predict Y-90 activity based on late arterial phase CECT imaging. Future work will include incorporation of more training data, fine-tuning of network hyperparameters to provide a more generalizable output and an ability to iterate the injection point for treatment planning.

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40-B DIET-INDUCED CHANGES IN THE TUMOR MICROENVIRONMENT AND METABOLIC LANDSCAPE PROMOTE HEAD AND NECK SQUAMOUS CELL CARCINOMA PROGRESSION AND INFLUENCE IMMUNOTHERAPY RESPONSE IN MURINE MODELS

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Head and Neck Squamous Cell Carcinoma (HNSCC) is associated with high morbidity and mortality. A Western Diet (WD) may promote cancer progression through inflammation and immunosuppression. We developed murine SCC cell lines derived from gain-of-function KrasG12D mutation and Smad4 deletion in keratin (K15)-positive stem cells closely mimicking the clinical progression of human HNSCC tumors. To investigate the effects of diet on SCC progression, SCC cells were orthotopically implanted into the buccal mucosa of C57BL/6 mice assigned to either regular diet (RD) or a Western diet. Tumors, saliva, cecum contents, liver, lungs, spleen, and plasma were collected at endpoint. Metabolomic profiling, spatial transcriptomics (NanoString GeoMx DSP), histopathology, immunohistochemistry, and multiplex immunofluorescence were performed. In a subsequent immunotherapy (anti-PD-L1) study, SCC cells were implanted orthotopically and subcutaneously into 8-10-week old C57BL/6 mice receiving RD or WD. Two days post tumor implantation, mice received anti-PD-L1 intraperitoneally (IP) three times weekly for two weeks. Mice were followed for survival and classified as responders (R) or nonresponders (NR). Responders with complete regression of both tumors were rechallenged to assess durable antitumor immunity. Oral tumor-bearing mice fed a WD exhibited more aggressive tumor progression, as indicated by increased tumor volume and histopathological features, compared with RD controls. WD tumors also displayed increased cancer stem cell signatures. Spatial transcriptomics revealed compartment-specific effects of WD, with reduced macrophage and fibroblast signatures in the stroma and enrichment of mitotic, cell-cycle, and DNA replication pathways in the tumor compartment, consistent with increased proliferation and more aggressive tumor growth and histology. Saliva from WD tumor-bearing mice exhibited distinct metabolite profiles of host and microbial origin. In the male SCC model, WD-fed mice exhibited greater weight loss and poorer body composition than RD controls, whereas an opposite trend was observed in female SCC models. In the context of anti-PD-L1 immunotherapy, WD was associated with a trend toward reduced treatment response. Together, these findings suggest that WD promotes a tumor-supportive environment through alterations in the TME and metabolomic landscape and may influence immunotherapy response. These results highlight diet as a potentially modifiable factor in HNSCC progression and treatment response, warranting further investigation.

41-A DEFINING MECHANISMS OF YAP1 DRIVEN HIGH-GRADE COMPLEX KARYOTYPE SARCOMAS

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Sarcomas are rare and heterogeneous connective tissue cancers consisting of more than 70 subtypes. There is an overall survival rate of 65% despite intensive therapy. High-grade sarcomas are categorized into two distinct groups: simple karyotype, which is driven by a translocation, and complex karyotype, which lacks a translocation and accounts for 85% of all sarcomas.

Yes associated protein 1 (YAP1) is a downstream regulator of the Hippo signaling pathway and is amplified across human sarcomas. It lacks a DNA-binding domain and requires transcriptional coactivators like TEA domain (TEAD) to regulate gene expression. Although it is mostly known to interact with TEAD, it can bind to other transcription factors. Our lab performed a genetic screen informed by The Cancer Genome Atlas (TCGA) and identified YAP1 as a potential driver of sarcoma development. We hypothesize that YAP1 is a driver of high-grade complex karyotype sarcomas through both TEAD-dependent and TEAD-independent mechanisms.

To evaluate TEAD-independent mechanisms, we utilized S94A YAP mutant which disrupts the YAP1-TEAD interaction. Empty vector (EV), wild-type YAP1, and S94A YAP were introduced into RB1-/- TP53+/- cells (the human sarcoma model developed by our lab in which RB1 and TP53 are knocked out in human immortalized MSC), spinfected, sorted, and injected into NSG mice. Tumors formed from cells expressing both wild-type YAP1 and S94A YAP1, indicating YAP1 has both TEAD-dependent and TEAD-independent mechanisms. The histology showed undifferentiated pleomorphic sarcomas (UPS) in the wild-type YAP1, while the S94A YAP1 revealed diverse histology – UPS, myxofibrosarcoma (MFS), rhabdomyosarcoma, and leiomyosarcoma. To identify potential non-TEAD transcriptional coactivators of YAP1, we utilized BioID proteomics analysis. Using Motif enrichment analysis, we identified seven potential transcription factor motifs. We are currently working to knock out these candidate genes and express YAP1 to evaluate their role in transformation in vitro using soft agar. Our results demonstrate that YAP1 functions as a driver through TEAD-dependent and TEAD-independent mechanisms. Our ongoing goal is to identify transcriptional coactivators required for YAP1 sarcoma development. These studies provide a better understanding about the role and mechanism of YAP1 in sarcoma development and will inform innovative therapies for this aggressive disease.

42-B THE HELICAL DOMAIN OF BRCA2 ACTS AS A STRUCTURAL ANCHOR TO COORDINATE MULTIVALENT DNA ENGAGEMENT

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The BRCA2 tumor suppressor maintains genome integrity through homologous recombination (HR), replication fork stabilization, and the suppression of error-prone mutagenic repair. A BRCA2 mutation carries a clinical burden, increasing risks for ovarian, breast, prostate, pancreatic, and other cancers. On the other hand, BRCA-deficient tumors offer personalized treatment options that exploit tumor-specific vulnerabilities. The majority of reported genetic alterations in the BRCA2 gene are variants of uncertain significance (VUS). VUS are non-informative for risk assessment and clinical management, creating a need to better evaluate BRCA2 VUS. Structurally, BRCA2 has a complex architecture of multiple distinct DNA-binding modules distributed across its N-terminus (NT) and a highly conserved C-terminal

domain (CTD) containing a helical domain (HD), OB folds, and a Tower domain. Clinical variants spanning both the NT and CT regions impair HR-mediated DNA repair. This suggests long-range structural coupling within BRCA2 that is not captured by the local domain organization alone. We investigated the role of inter-domain cooperation in BRCA2 DNA binding using BRCA2 protein and isolated N-terminal and C-terminal fragments (BRCA2NT and BRCA2CT) to determine different substrate affinities. Our results showed that both the BRCA2 protein and individual fragments display a distinct preference for longer single-stranded DNA (ssDNA) substrates; the combined NT and CTD fragments show significantly reduced affinity compared to the intact BRCA2. Furthermore, the Tower-deleted CT fragment retains robust DNA binding and specifically binds to dsDNA to possibly provide ssDNA-dsDNA junction specificity. Deletion of the HD completely abolishes DNA binding, identifying the HD as a vital structural anchor required to align these distant modules. Interestingly, the HD represents a hotspot for pathogenic point mutations, underlining its functional significance. Together, these results support a model in which BRCA2 engages DNA through cooperative, multivalent interactions requiring structural integrity across distant domains. The predicted structural failure of HD mutations impairs downstream HR, DNA replication, and TMEJ suppression, exposing a potential molecular vulnerability that specifically sensitizes HD-mutant cells.

43-A METABOLOMIC AND LIPIDOMIC PROFILING REVEALS DISTINCT SUBTYPES OF GLIOBLASTOMA IDH-WILDTYPE AND SHARED METABOLIC FEATURES WITH ASTROCYTOMA IDH MUTANT GRADE 4

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Background: Glioblastoma is a metabolically diverse and aggressive brain tumor. We used untargeted metabolomics and lipidomics with supervised analysis to define metabolic changes within IDH-wildtype glioblastoma and IDH-mutant astrocytoma, grade 4, as well as to identify potential subclusters of metabolically distinct tumor types.

Methods: Brain tissue from IDH-wildtype glioblastoma (n = 38), IDH-mutant astrocytoma, Grade 4 (n = 5), and non-neoplastic controls (n = 20) underwent untargeted metabolomic and lipidomic profiling. Partial Least Squares Discriminant Analysis was followed by k-means clustering. ANOVA was used to identify significantly altered metabolites, with significance defined as fold change (FC) of greater than 2 and p-value correction based on a false discovery rate of 0.05. Heatmaps visualized differences, and pathway enrichment was performed using MetaboAnalyst 6.0.

Results: Glioblastoma exhibited numerous significantly altered metabolites and lipids compared to controls, including increases in hypotaurine (FC 5.5, p = 9×10^{-5}) and sorbitol (FC 3.9, p = 0.003), and decreases in ribonic acid (FC -3.3, p = 1.6×10^{-13}) and arabitol (FC -2.9, p = 4.1×10^{-20}). K-means clustering revealed three distinct metabolic subtypes within IDH-wildtype glioblastoma. Cluster 1 showed increased galactose (p=0.02) and sucrose metabolism (p=0.009). Cluster 2 was characterized by increased glutathione metabolism (p=0.002). Cluster 3 demonstrated increased arginine biosynthesis (p= 7.5×10^{-4}). IDH-mutant tumors exhibited 130-fold elevated levels of 2-hydroxyglutarate (2HG). Lipidomic profiling demonstrated numerous altered lipids in both tumor types compared to controls, including increases in sphingomyelin 40:1 (FC 157, p= 4.4×10^{-5}) and decreases in phosphatidylcholine 39:7 (FC -2.8, p= 3.0×10^{-19}), but overall similar lipidomic profiles between the two tumor types.

Conclusions: Metabolomic profiling identified three distinct subtypes of IDH-wildtype glioblastoma with unique metabolic signatures and revealed shared metabolic features between glioblastoma and IDH-mutant astrocytoma grade 4. These results highlight the potential for metabolic classification to improve understanding of tumor biology and guide personalized treatment strategies for patients.

44-B A NOVEL PROHIBITIN LIGAND PREVENTS THE FORMATION OF MITOCHONDRIAL TRANSFER-RELATED TUNNELING NANOTUBES AND SENSITIZES MODELS OF METASTATIC PROSTATE CANCER TO ANDROGEN RECEPTOR SIGNALING INHIBITORS

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Metastatic bone disease (MBD) causes morbidity and mortality in prostate cancer (PCa) patients. PCa is largely driven by the nuclear hormone receptor androgen receptor (AR) that acts as a transcription factor to regulate tumor growth and metastasis. Hence, MBD in PCa patients is often treated with AR signaling inhibitors (ARSI), but patients eventually develop resistance to this therapy. The overall goal of the present study is to devise new therapy to prevent this resistance. Cancer cells can undergo intercellular mitochondrial transfer (IMT) from other cells in the tumor microenvironment to support metabolism for tumor growth, therapy resistance and metastasis. Here, we hypothesize that IMT plays a role in MBD promotion and in resistance to ARSI. Various studies report the development of intercellular or “tunneling” nanotube (TNT) in the transfer of mitochondria between stromal and tumor epithelial cells. The current project investigates the role of mitochondria-transferring TNTs in ARSI resistance in a model of MBD. We identified the scaffolding molecule prohibitin (PHB) as a novel mediator of IMT in TNT formation. PHB is normally expressed in the inner mitochondrial membrane (IMM) while mislocalization to the outer mitochondrial membrane (OMM) triggers mitophagy. We previously demonstrated that the AR is a negative regulator of PHB, while PHB in turn suppresses AR transcriptional activity. We now show that loss of PHB expression enhances AR transcriptional activity, but destroys mitochondrial biogenesis, and promotes TNT formation. Paradoxically, loss of AR transcriptional activity also promotes TNT formation suggesting that imbalance in PHB expression destabilizes mitochondrial biogenesis and promotes TNT formation. A novel PHB ligand that increases PHB expression was shown to prevent TNT development. It also inhibited AR transcriptional activity and caused mitophagy-induced cell death and cell migration. The ligand showed low toxicity in immunocompetent mice and suppressed tumor growth. Further, it sensitized the MBD model PCa cells to ARSI. These results suggest that the novel PHB ligand may be used to prevent TNT formation, which in turn inhibits IMT, thereby sensitizing MBD to ARSI treatment.

45-A INVESTIGATING THE CANCER-ASSOCIATED MUC1 GLYCOPROTEIN IN EXTRACELLULAR VESICLE BIOGENESIS

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Extracellular Vesicles (EVs) are lipid membrane-bound nanoparticles which contain bioactive cargo, including DNA, RNA and proteins, and which are released by nearly all cell types making them key mediators of intercellular communication. Similarly, the glycocalyx, a “sugar” coating on the outer membrane of cells, also acts as a key regulator of intercellular communication regulating chemical, electrical, and immunological signals. Cancer cells are known to exhibit an altered glycocalyx and secrete more EVs than their healthy counterparts. However, the extent to which the glycocalyx regulates EV biogenesis remains poorly understood. A major component within the glycocalyx, Mucin-1 (MUC1), is an extensively O-glycosylated glycoprotein that is known to be overexpressed in many types of cancers including lung, liver, pancreatic, breast and ovarian cancer. Our lab has previously reported that overexpression of bulky glycocalyx biopolymers, including MUC1, can promote EV secretion. Here, we investigate EVs from suspension-adapted cells expressing a MUC1-enriched cancer-like glycocalyx and summarize our recent efforts to characterize the secretion and protein content of these EVs using nanoparticle tracking analysis, along with proteomics analysis and validation of selected canonical EV markers by western blot. Nanoparticle tracking analysis indicated an expression-dependent relationship between cell-surface MUC1 and EV secretion wherein higher levels of cell-surface MUC1 would increase EV secretion while proteomic profiling of MUC1-enriched EVs versus control EVs showed an enhanced plasma membrane-inner leaflet budding lineage thereby shifting EV biogenesis towards the plasma membrane. Overall, this study shows how MUC1 expression can alter EV secretion and biogenesis. These findings improve our understanding of how the cancer-associated glycocalyx directly regulates the release of EVs and simultaneously influences their biology. This provides a framework for future studies investigating the effects of other cancer-associated glycocalyx changes on EV biogenesis and function.

46-B CD101 LOSS RESTRICTS HEAD AND NECK SQUAMOUS CELL CARCINOMA PROGRESSION INDEPENDENT OF GLOBAL TME LINEAGE RECRUITMENT

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Immune checkpoint blockade has transformed treatment for head and neck squamous cell carcinoma (HNSCC), yet many patients fail to achieve durable responses due to microenvironmental immune suppression. CD101, an inhibitory surface receptor expressed across immune population subsets, has emerged as a potential regulator of tumor progression. Here we investigated how CD101 loss impacts longitudinal tumor growth kinetics and survival in vivo as well as spatial microenvironmental organization.

Wild-type (WT) and CD101 knock-out (KO) murine HNSCC models were evaluated for longitudinal tumor growth kinetics and overall survival. High-plex spatial transcriptomics with unsupervised clustering was performed to delineate spatial niches and evaluate global tumor microenvironment (TME) cellular composition across WT and KO tumors.

CD101 is expressed at a high level in HNSCC compared to other tumor types according to the Cancer Genome Atlas Program (TCGA). It is expressed primarily on immune cells, with similar expression between clinical samples and our murine A223 HNSCC murine model as assessed by single-cell RNA sequencing. CD101 KO mice exhibit a statistically significant reduction in A223 tumor burden compared to WT controls, along with a trending increase in overall survival. Unsupervised spatial transcriptomic analysis revealed that global TME lineage composition remains conserved between WT and KO tumors.

CD101 loss significantly restricts HNSCC tumor burden and improves survival trends without disrupting overall cellular recruitment in the TME. While broad lineage composition remains conserved, CD101 loss appears to modulate localized cellular functional states. To define the localized drivers of tumor growth, ongoing analysis using spatial transcriptomic profiling is focused on evaluating cluster-specific differentially expressed genes within distinct spatial niches.

47-A INTEGRATIVE TRANSCRIPTOMICS AND METABOLOMICS IDENTIFY DIFFERENCES IN METABOLIC PATHWAYS IN INVASIVE VS NON-INVASIVE BLADDER CANCER IN OLDER MALE PATIENTS

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Background: ~70% of patients with bladder cancer (BICa) are initially detected with non-muscle-invasive bladder cancer (NMIBC); however, they often progress to muscle-invasive bladder cancer (MIBC), which are more likely to metastasize and are often indicative of poor survival. Integrative transcriptomics and metabolomics studies are increasingly being used to link gene expression to functional biochemical outcomes, mapping entire biological pathways from gene to product and reducing false positives. Here, we have used this approach to identify differentially activated pathways in invasive vs non-invasive tumors in patients with BICa.

Methods: Fresh frozen tumor tissues from 46 patients who underwent surgery at University of California Davis (UC Davis) between 2011-2018 were obtained from the UC Davis Comprehensive Cancer Center (UCDCCC) Biorepository and subjected to untargeted metabolomic analysis to detect primary metabolites, biogenic amines and complex lipids. RNA-sequencing from a subset of 14 patients were used to identify corresponding genes. Patient characteristics were determined by accessing the Electronic Medical Records (EMR).

Results: We identified the metabolites that were differentially expressed in male vs female, young (<60) vs old (≥60), chemotherapy vs no chemotherapy, smokers vs non-smokers, obese vs non-obese, high- vs low-grade, invasive vs non-invasive and metastatic vs non-metastatic with adjusted p-value <0.05 and log2fold-change ≥±1.2. Further categorization showed significant different metabolites (n=467) in invasive (n=28) vs non-invasive (n=9) tumors only in the ≥60 group. Transcriptomics data was similarly compared from invasive (n=10) vs non-invasive (n=4) tumors and matched to the metabolomics data using Metaboanalyst 6.0 joint pathway analysis, which identified 5 pathways that contained both genes and metabolites that fulfilled our criteria [Nicotinate and nicotinamide metabolism (AOX1, CD38, NMNAT2 mapped to 1-Methylnicotinamide and NAD), purine metabolism (PDE10A, PDE11A, ENTPD8 mapped to AMP), histidine metabolism (AOC1, HDC, CNBP1 mapped to histamine), fructose and mannose metabolism (HKDC1 mapped to D-fructose), and arginine and proline metabolism (PRODH mapped to L-Proline)]. Gene expression was validated against TCGA database to show that only the purine metabolism pathway matched publicly available data.

Conclusions: Fast-growing BICa cells rely heavily on de novo purine synthesis to supply building blocks for nucleic acids. They will be the target of investigation in future studies.

48-B OBESITY PROMOTES TUMORIGENESIS IN A TREATMENT-NAÏVE SYNGENEIC MOUSE MODEL OF TNBC BUT INCREASES ANTI-PD-1 EFFICACY

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Obesity and breast cancer (BCa) rates have more than doubled since 1990. While obesity (BMI $\geq$ 30 kg/m²) is an established risk factor for hormone-positive (HR+) BCa, its impact on treatment of TNBC is unknown. Thus, we sought to determine the effect of obesity in TNBC tumorigenesis and response to anti-PD-1 therapy in a syngeneic mouse model. Mice fed either a 60% kcal high fat diet (HFD) or a control diet (CD) for 14 weeks received 500K E0771GFP/Luc cells orthotopically implanted into the mammary fat pads. Tumor growth and metastasis was quantified using in vivo imaging 2x/week. When tumors reached $\sim$ 300 mm³, anti-PD-1 therapy or isotype control (5 mg/kg) was initiated 2x/week up to humane end points when primary and metastatic tumors were collected for flow cytometry and immunofluorescence. We found that the tumor engraftment rate for mice on HFD was 95.8% compared to 45.8% for CD mice, indicating that obesity results in a more favorable microenvironment for tumor implantation; tumors of HFD mice also reached dosing criteria (300mm³) significantly faster than those on CD. Interestingly, HFD mice treated with anti-PD-1 demonstrated significantly increased survival as compared to isotype control-treated, or mice on the CD treated with anti-PD-1 suggesting that while obesity increases tumorigenic rate, it improves anti-PD-1 efficacy and extends survival. Ex vivo imaging data revealed that while mice on HFD responded to anti-PD-1 therapy and reduced primary tumor size, metastatic spread persisted as most mice harbored liver, lung, and bone metastatic lesions. Immunofluorescence revealed elevated expression of several ECM-derived molecules such as collagen 4 and collagen 6 in tumors from mice on HFD as compared to a CD, suggesting that an obese microenvironment may promote anti-PD-1 efficacy by changing biomechanical properties of the ECM. Moreover, there was enhanced expression of CD4/CD8 T-cells in anti-PD-1 treated mice as compared to isotype, with HFD mice showcasing dense populations of CD4/CD8 T-cells within the core of the tumor. Future studies are in progress to identify other mechanisms or cell populations that may be responsible for the improved efficacy of anti-PD-1 in diet-induced obese mice.

49-A AI/ML-BASED MULTIMODALITY CHARACTERIZATION OF CANINE HEPATOCELLULAR CARCINOMA (HCC): A TRANSLATIONAL APPROACH FOR IMPROVED DIAGNOSIS, PROGNOSIS AND TREATMENT

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Multiple analytical modalities offer valuable insights but are often used separately, limiting their utility in studying complex diseases like cancer and highlighting the need to integrate them. Recent advances in Artificial Intelligence/Machine Learning (AI/ML) approaches can be employed not only to automate individual modality analysis but also to integrate results across modalities, yielding unified, more powerful results for greater accuracy/efficiency. To this end, we have studied radiology, histology, proteomics, transcriptomics, and tissue/blood biomarkers with the aim of integrating them using AI/ML to investigate the molecular/cellular pathogenesis of canine hepatocellular carcinoma (HCC) as a natural translational model of human HCC. We are developing an automated analysis for deploying AI/ML-based solutions for clinical decision support (CDS). Results of the multimodal analyses of canine HCC in an ongoing collaborative study between UC Davis School of Medicine and the Veterinary School will be presented.

50-B CUPROPTOTIC PRESSURE RESULTS IN TUMOR-INTRINSIC MHC-I UPREGULATION AND SENSITIZES ORAL SQUAMOUS CELL CARCINOMA TO ANTI-PD-L1

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Background. Oral squamous cell carcinoma (OSCC), the leading form of head and neck cancer, has dismal outcomes for recurrent/metastatic disease, with 5-year survival historically below 10%. Response rates to PD-1/PD-L1 immune checkpoint inhibitors (ICI) are less than 20%, highlighting the need to improve immunotherapy efficacy. Cuproptosis, a recently identified copper-dependent form of regulated cell death, has been studied almost entirely as an immunogenic cell death (ICD) endpoint. Growing evidence suggests that cuproptosis synergizes with ICI through immune recruitment in cuproptosis-responsive tumor models. Despite readily killing tumor cells in-vitro, cuproptosis inducers yield only transient growth delay and fail to eradicate OSCC tumors as single agents in-vivo. We asked whether tumor-intrinsic responses to cuproptotic pressure may sensitize tumors to ICI, improving therapeutic efficacy.

Methods. A223 OSCC cells treated with elesclomol-Cu(II) (eles-Cu), a cuproptosis inducer, were profiled by bulk RNA-seq with transcription-factor and pathway analysis and 68-plex cytokine secretion (also assayed for a second OSCC line, A1419); cuproptosis was confirmed by DLAT oligomerization on western blot. In-vivo, syngeneic A223 and A1419 tumors ($\pm$ eles-Cu, $\pm$ anti-PD-L1) and athymic-nude A223 tumors were assessed for growth, survival, and multiplex immune infiltrate.

Results. Under cuproptotic pressure, A223 cells upregulated B2m, MHC-I heavy chains (H2-K1/H2-D1), and the transactivator Nlr5, alongside increased NF- κ B/NF- γ activity. Decreased STAT1 activity and without induction of IFN- γ or IFN- β in cell culture supernatants suggested interferon-independent antigen presentation. Unbiased GSEA ranked antigen-processing and interferon-response gene sets among top enrichments, consistent with non-interferon program converging on shared target genes rather than IFN-STAT1 signaling. Functionally, eles-Cu sensitized A223 tumors to anti-PD-L1, and combined eles-Cu/anti-PD-L1 treatment slowed tumor growth in A1419. This also resulted in increased intratumoral T cell infiltration. Benefits were abrogated in athymic nude mice, establishing T-cell dependent antitumor effects.

Conclusions. Cuproptotic pressure elicits a tumor-intrinsic, interferon-independent antigen-presentation program in OSCC cells that are

sensitized to anti-PD-L1 in a T-cell-dependent manner across two OSCC models. This distinguishes an intrinsic adaptive arm from the extrinsic ICD arm described for cuproptosis. Cuproptosis inducers may improve the therapeutic efficacy of ICI, and further elucidation of causal links is warranted. (Funding: CO HNC SPORE P50-CA261605)

51-A FLOW CYTOMETRIC DISTINCTION OF PURE ERYTHROID LEUKEMIA FROM CONVENTIONAL ACUTE MYELOID LEUKEMIA: A SINGLE-INSTITUTION EXPERIENCE

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Background: Pure erythroid leukemia (PEL) is a rare and aggressive subtype of acute myeloid leukemia (AML) characterized by a predominance of immature erythroid precursors. Morphologic distinction between neoplastic pronormoblasts and myeloid blasts can be challenging, particularly in cases with poorly differentiated cells, overlapping cytologic features, or limited bone marrow material and may lead to difficulty distinguishing PEL from conventional AML. Multiparameter flow cytometry serves as a valuable adjunct by identifying lineage-specific and aberrant antigen expression patterns, facilitating accurate classification in diagnostically challenging cases. Here, we describe our institutional experience comparing the flow cytometric immunophenotypic features of PEL with conventional AML to define characteristics that aid in their distinction.

Methods: We retrospectively reviewed patients diagnosed with PEL at our institution and compared their multiparameter flow cytometric findings with a cohort of non-PEL AML cases evaluated during the same period. Expression patterns of erythroid-associated markers (CD71, CD117, CD235a, CD38, CD4, CD45) and myeloid-associated antigens (CD34, CD13, CD33, CD117, HLA-DR, CD7, CD56, MPO) were analyzed.

Results: Neoplastic erythroid cells in all PEL cases demonstrated uniform expression of CD71 with dim CD45 expression relative to granulocytes. CD117 expression ranged from partial to uniform, while CD235a expression was largely restricted to the more differentiated CD117-dim/negative erythroid subset. Compared with conventional AML blasts, PEL erythroid precursors consistently lacked CD34, HLA-DR and myeloperoxidase (MPO) expression despite their immature morphology. Markedly decreased or absent CD38 expression was a characteristic feature of PEL and was uncommon in AML blasts. Aberrant CD4, CD7 and CD13 expression on erythroid precursors represented lineage-inappropriate antigen expression. In contrast, conventional AML blasts typically expressed CD34, CD13, CD33, CD117, HLA-DR (subtype-dependent), and/or MPO without erythroid-associated coexpression of CD235a and CD71. Notably, despite the absence of CD34 on neoplastic erythroid cells, a distinct population of CD34-positive myeloid blasts was identified in most PEL cases. These blasts were not numerically increased but exhibited aberrant immunophenotypic features, including asynchronous antigen expression and abnormal maturation patterns.

Conclusions: Our institutional experience demonstrates that PEL exhibits a distinctive flow cytometric immunophenotype characterized by aberrant antigen expression on neoplastic erythroid precursors and a phenotypically abnormal but quantitatively non-expanded CD34-positive myeloid blast population.

52-B WOUND-ASSOCIATED KERATINOCYTE PROGRAMS DISTINGUISH MELANOMA FROM MELANOCYTIC NEVI

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Melanoma, one of the deadliest skin cancers, can be cured if diagnosed early. However, accurate diagnosis can be challenging because a subset of melanomas resemble benign melanocytic nevi clinically and histologically, leading to delayed or missed diagnoses. Early melanomas are confined to the epidermis, the uppermost layer of the skin composed of keratinocytes. However, the role of keratinocytes in the initiation and progression of melanoma in addition to their potential utility for biomarker discovery is largely unexplored. In this study, we used single-cell spatial transcriptomics to profile the expression of approximately 6000 genes within 147,541 cells of the tumor microenvironment of melanomas and melanocytic nevi (three invasive melanomas, one melanoma in situ, one dysplastic nevus, one common nevus, and one basal cell carcinoma). For each sample, sections containing both lesional and adjacent non-lesional epidermal tissue were analyzed. Differential gene expression analysis comparing lesional and non-lesional keratinocyte niches revealed increased expression of damage-associated molecular patterns (DAMPs) S100A7, S100A8, and S100A9 and wound-associated keratins (KRT6B and KRT6C) in the microenvironment of melanoma and basal cell carcinoma, but not nevi. Protein-level validation by immunohistochemistry of KRT6 in melanomas (n=3) and nevi (n=3) demonstrated a 26-fold higher median epidermal KRT6-positive area in melanomas compared with nevi (10.2% vs 0.4%; normal skin 0.16%), with every melanoma exceeding every nevus (two-sided Mann-Whitney U test, p=0.10, the minimum attainable value at n=3 per group; rank-biserial correlation r=1.0, indicating complete rank separation). Together, these findings identify a distinct keratinocyte response within the melanoma microenvironment and support further investigation of keratinocyte-derived signals, including KRT6, as potential biomarkers for melanoma diagnosis.

53-A INVESTIGATING THE CHOP MEDIATED ER STRESS RESPONSE ON SARCOMA DEVELOPMENT

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Sarcomas are a group of rare and heterogeneous tumors of mesenchymal origin. Previously, our lab established a model for sarcoma development that reflects the human disease. Using a genetic screen informed by the cancer genome atlas (TCGA) we identified C/EBP homologous protein (CHOP) as a potential driver of sarcoma development. Interestingly, CHOP alone was not able to drive sarcoma formation, but addition of CHOP to other oncogenic drivers such as YAP1 resulted in a more aggressive phenotype. CHOP is a downstream effector of the unfolded protein response (UPR) which is activated during ER stress. Its known transcriptional targets are endoplasmic reticulum oxidoreductase 1 alpha (ERO1a), tribbles pseudokinase 3 (TRIB3), growth arrest, and DNA damage-inducible protein 34 (GADD34) and death receptor 5 (DR5), which help mediate elevated levels of ER stress.

To understand how CHOP facilitates sarcoma development, we used CRISPR CAS9 to deplete known downstream targets ERO1 α -/-, DR5-/-, GADD34-/- and TRIB3-/- in our YAP1-CHOP model. Surprisingly, loss of these targets did not ablate the in vivo phenotype, instead, ERO1 α -/-(+YAP1-CHOP) and TRIB3-/-(+YAP1-CHOP) resulted in more aggressive tumor formation. To investigate whether there is transcriptional regulation across any of the downstream targets, we assayed target gene expression in our KO cell lines. Interestingly, transcript levels were significantly decreased for ERO1 α , DR5, and TRIB3, suggesting they may regulate each other. Next, we assayed transcript levels of CHOP and its transcriptional activator, ATF4, to determine whether they may be compensating for the loss of these targets. Unexpectedly, both CHOP and ATF4 were significantly reduced, indicating another target may be regulating these genes. Finally, to understand how ERO1 α loss influences a more aggressive phenotype we conducted a reactive oxygen species assay (ROS). ERO1 α -/-(+YAP1-CHOP) resulted in a significant increase in ROS compared to ERO1 α -/- cells implying that despite loss of ERO1 α YAP1-CHOP may mediate cellular stress. We are currently working to identify key points of regulation of the CHOP transcriptional program.

Understanding the role of CHOP during sarcoma development is critical to developing needed therapies for this disease.

54-B LANDSCAPE OF STRUCTURAL REARRANGEMENTS IN MISMATCH REPAIR-DEFICIENT CANCERS

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A significant fraction of cancers impacting high turnover tissues such as the skin, colon, and endometrium are caused by loss of mismatch repair. In somatic cells, post-replicative mismatch repair is primarily dependent on MSH2, MSH6, MLH1, and PMS2. The MSH2-MSH6 heterodimer slides along the newly synthesized DNA and detects base-base mismatches and small insertions/deletions, then recruits MLH1-PMS2 to excise the erroneous bases. Mutation or loss of expression of any component of this pathway results in a mutator phenotype characterized by base/base mismatches and insertions/deletions, and can also cause microsatellite instability, in which microsatellite repeats expand or contract. Loss of mismatch repair is thought to drive tumorigenesis through an accumulation of mutations in key tumor suppressors and/or oncogenes. This accumulation of base changes results in the formation of numerous neoantigens, making them an ideal target for anti-PD1/PD-L1 therapies.

Although generally associated with more favorable outcomes than mismatch repair-proficient tumors, approximately half of all mismatch repair-deficient tumors eventually become resistant to anti-PD1/PD-L1 therapies through immunoediting, necessitating the development of alternative therapies. Towards this goal, we sought to comprehensively map the landscape of structural rearrangements across mismatch repair-deficient tumors. Whereas mutation in any one of the mismatch repair proteins is expected to lead to a mutator phenotype, only loss of function of MSH2 or MSH6 is expected to result in a unique mutational signature epitomized by intra-chromosomal structural rearrangements involving near-identical repeats such as transposable elements, segmental duplications, or sub-telomeric repeats. These short-range structural variants form through loss of regulation of the homologous recombination DNA repair pathway by MSH2-MSH6, which identifies sequence heterologies in recombination pairing intermediates and triggers their reversal.

While this pattern of structural rearrangements in MSH2/6-deficient tumors is strongly predicted from genetic studies in yeast, mice, and human cells, it has not yet been discovered in patient-derived tumors due to the inability of short-read sequencing to identify structural rearrangements between highly similar DNA repeats. Herein, we used Severus to detect tumor-specific structural variants in patient tumors relative to matched healthy tissue controls. We present a preliminary analysis of several mismatch repair-deficient colorectal cancers and a single sebaceous adenocarcinoma.

55-A SINGULARITIES IN GROWTH CONTROL SYSTEM

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Embryogenesis builds every organ through a network of organizers—local singularities that pattern growth and form. Developmental logic dictates that this growth-control network is not dismantled at birth: maintenance, regeneration, and lifelong regulation of tissue architecture require its persistence. This postembryonic growth control system is foundational, partly embedded with and partly independent of neurohumoral signaling. Biophysical and morphological features suggest acupoints arise from these organizers. Evidence converges from acupoint stimulation (AS): low-intensity, non-thermal laser produces therapeutic and growth-regulating effects without activating peripheral nerves or reorganizing collagen, and local purinergic and nitric oxide signaling—pathways that predate the nervous system—initiate responses requiring neither intact nerves nor connective tissue. These primordial pathways exert bidirectional, normalizing effects on proliferation, senescence, apoptosis, and inflammation. The framework makes testable predictions, several already partially confirmed. Foremost, the model predicts AS should re-engage the developmental organizer machinery—now documented: AS regulates canonical morphogen and organizer pathways, including Wnt/ β -catenin and Sonic hedgehog (Shh) signaling, and mobilizes resident stem and progenitor cells, the effectors of embryonic growth control. These growth-control effects far exceed those of an analgesic or reflex stimulus.

The system is organized around singularities: extreme points of body-surface curvature, internal tissue-interface curvature, and boundaries between body domains, coinciding with acupoints (organizer remnants) and connective-tissue planes. As predicted, singularities are physically distinguishable—measurably higher electrical conductance and lower impedance, elevated nitric oxide—serving as accessible readouts of the underlying network. Therapeutically, they offer disproportionate leverage: perturbation at a singular node yields systemic effects far exceeding non-singular points, explaining how small stimuli cause large, durable change.

This reframes AS as singularity perturbation: controlled inputs at sensitive nodes that renormalize a malfunctioning system, not inhibition of single pathways. Because it depends on the self-organizing capacity of a conserved network, the model predicts declining responsiveness with age and chronicity, consistent with clinical observation. That independent confirmations on organizer-pathway activation, the physical signature of singularities, and age-dependent responsiveness give the framework empirical traction beyond plausibility. Mapping/measuring these singularities and optimizing perturbation parameters opens a mechanistically grounded avenue for diagnosis and therapy—including in oncology, where dysregulated growth control is the focus.

56-B INTEGRATED MIRNA–MRNA ANALYSIS IDENTIFIES CANDIDATE REGULATORY NETWORKS ASSOCIATED WITH P53 R273H-MEDIATED RADIATION RESPONSE IN PROSTATE CANCER

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Radiation therapy is an important treatment for prostate cancer, but radiation resistance can limit treatment effectiveness. The tumor suppressor p53 plays a critical role in the cellular response to DNA damage, and mutations such as R273H may alter these responses. This study aimed to identify miRNAs and mRNAs associated with differential radiation responses in parental LNCaP and LNCaP-R273H prostate cancer cells and to identify candidate miRNA-mRNA regulatory networks that may contribute to radiation resistance.

miRNA and mRNA microarray data were analyzed from parental LNCaP and LNCaP-R273H prostate cancer cells exposed to either 0 Gy or 10 Gy radiation. Four comparisons were performed: LNCaP 0 Gy versus 10 Gy, LNCaP-R273H 0 Gy versus 10 Gy, LNCaP versus LNCaP-R273H at 0 Gy, and LNCaP versus LNCaP-R273H at 10 Gy. miRNAs and mRNAs exhibiting at least 1.5-fold changes in expression were identified. miRDB was used to identify predicted mRNA targets of the identified miRNAs, and predicted targets were cross-referenced with mRNAs identified in the corresponding microarray comparisons. Genes identified both as predicted miRNA targets and as altered in the mRNA datasets were designated as common genes and prioritized for pathway and miRNA-mRNA regulatory network analyses.

Fold-change analysis identified 93 miRNAs with at least 1.5-fold differences in their radiation-associated expression changes between LNCaP-R273H and parental LNCaP cells. Multiple inverse relationships between miRNA and predicted target mRNA expression were identified. Notably, altered miR-34a expression was associated with expression changes in 10 predicted target mRNAs, including AR, SIRT1, CCNE2, JAG1, TP53INP2, MAP3K14, PEG10, NAV3, MID1, and ALCAM.

These findings identify candidate miRNA-mRNA regulatory relationships that may contribute to R273H-associated alterations in the prostate cancer cell response to radiation and provide a foundation for investigating mechanisms of radiation resistance. Candidate miRNAs and mRNA targets will be further validated using qRT-PCR and Western blotting.

57-A TRAFFIC-RELATED AIR POLLUTION EXPOSURE DRIVES BREAST CANCER PROGRESSION AND IMMUNE REMODELING OF THE TUMOR MICROENVIRONMENT VIA AHR

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Traffic-related air pollution (TRAP) is a dynamic mixture of gases and particulate matter (PM) emitted from motor vehicles. TRAP exposure is one driver of environmental injustice, with highest exposure in communities of color and communities with low socioeconomic status. Recent epidemiological studies have revealed a link between TRAP exposure and breast cancer incidence. The Aryl Hydrocarbon Receptor (AhR) is a ligand-activated transcription factor with an oncogenic role in breast cancer. Of note, AhR is activated by components of TRAP, including polycyclic aromatic hydrocarbons (PAHs). In this study, we examined the impact of TRAP exposure on mammary tumorigenesis in the Polyoma Middle T (PyMT) mouse model of breast cancer. Mice exposed to real-time TRAP in the Caldecott Tunnel exposure facility show significantly decreased tumor-free survival, higher tumor burden and increased lung metastasis. The impact of TRAP is blunted in PyMT mice overexpressing the AhR repressor (AhRR), implicating AhR in TRAP's mechanism. Our results also indicate that TRAP exposure contributes to an immune suppressive tumor microenvironment with increased presence of myeloid derived suppressor cells and tumor associated macrophages.

58-B OPTIMIZATION OF CLUSTERING-BASED CELL PHENOTYPING FOR SPATIAL PROTEOMIC ANALYSIS OF BREAST CANCER BRAIN METASTASIS

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Breast cancer brain metastases (BrMets) are among the most devastating complications of metastatic breast cancer, resulting in substantial neurologic morbidity, diminished quality of life, and poor overall survival. Approximately 10–15% of patients with metastatic breast cancer develop BrMets, with incidence reaching 30% in HER2-positive and 50% in triple-negative breast cancer. Despite advances in treatment, the cellular composition and spatial organization of the brain metastatic microenvironment remain incompletely understood. Highly multiplexed spatial proteomics provides an opportunity to characterize this complex microenvironment at single-cell resolution; however, extracting biologically meaningful cell populations from these high-dimensional data requires robust and validated computational phenotyping approaches. Here, we evaluated a clustering-based cell phenotyping workflow using PhenoCycler Fusion spatial proteomic data generated with a 52-marker panel, across as 26-core tissue microarray. Initial workflow optimization was performed on four representative tissue cores: breast cancer BrMet (n=2) and non-cancer brain (n=2). Data were processed using the SPACEc (Spatial Analysis for CODEX Data) pipeline, including single-cell segmentation, quality control, and marker intensity normalization. Unsupervised clustering (Louvain algorithm) was then applied to group cells according to similarities in their protein expression profiles. Cluster-specific marker expression and spatial distributions were examined and compared with the original multiplexed tissue images to assess biological concordance. Unsupervised clustering identified distinct cellular populations with marker profiles consistent with the expected differences between the two tissue types. BrMet tissue contained clusters enriched for epithelial markers, including Pan-Cytokeratin, MUC1, GATA3, Keratin19, and EpCAM, whereas non-cancer brain tissues contained clusters enriched for neuronal markers such as Neurofilament and MAP2. Spatial mapping of these clusters showed correspondence to the locations of the respective markers in the original QTIFF images. These results suggest that unsupervised clustering can identify biologically interpretable cell populations across complex tissue images. Ongoing work focuses on refining cell clusters and cell-type annotations, and evaluating the robustness of the SPACEc workflow before applying it to the larger tissue cohort (n=235). This optimized framework will provide the foundation for subsequent analyses of cellular

composition and spatial organization, including cell-cell interaction and cell-type proximity analyses, to further characterize the BrMet microenvironment.

59-A TDA AND ML IMPLICATE NRG1-ASSOCIATED GENOMIC ALTERATIONS IN LUMINAL B BREAST CANCER

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Luminal B breast cancer is more aggressive than Luminal A breast cancer, but less than HER2 and Basal breast cancers. The chromosomal region 8p12 has been associated with genomic alterations in Luminal B, and deletions here are associated with poor prognosis, advanced tumor stage, and aggressive breast cancer. Also, within chromosome 8p12, there is a region which contains a single gene that is associated with cancer: NRG1. Here we study NRG1 and the genes that are close in proximity to it: TEX15, PURG, and WRN and suggest two reasons for the observed phenotypes: possible fusion candidates and associated molecular features. Using TCGA Luminal B data, we found optimal age and expression cutoffs using MaxStat, and NRG1, TEX15, PURG, and WRN expression and copy number, along with patient age, tumor stage, and node stage were tested for survival association using Cox regression and Kaplan-Meier analysis. High expression and low copy number data was used to identify candidate gene fusions involving NRG1 and confirmed via cBioPortal. We applied Principal Component Analysis to reduce dimensionality across subtypes and Random Forest and Gradient Boosting to classify subtypes and identify key features.

Our results show that high NRG1 expression is associated with worse survival by Kaplan-Meier analysis ($p = 0.000142$) and Cox regression ($p = 0.036$). This remains significant when accounting for the median age of the patients (60 years), tumor stage, and node stage ($p = 0.028, 0.018, 0.023$), but was lost when age was defined using a MaxStat-derived cutpoint (~ 67.9 years, $p = 0.058$), indicating that NRG1's significance is sensitive to how age is modeled. The same significance was not found for TEX15, PURG, or WRN. Our results also identified one NRG1 fusion, NRG1-AKAP13 via cBioPortal. In addition, TEX15 and ER-Status were identified by both the Random Forest and Gradient Boosting models as the most important features used to differentiate the subtypes. These findings align with prior reports that NRG1 is associated with worse survival and highlight that NRG1 is a fusion candidate in Luminal B breast cancer, and identify TEX15 status and ER-status as significant features across subtypes.

60-B METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA-DERIVED EXTRACELLULAR VESICLES FACILITATE TUMOR GROWTH AND METASTATIC NICHE FORMATION

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Introduction and hypothesis/objectives: HNSCC has high morbidity and mortality. Treatments are effective for early-stage disease, but outcomes for recurrent/metastatic disease remain poor, and existing biomarkers fail to predict metastasis. The lack of spontaneous lung SCC metastasis models in an immunocompetent background has hindered mechanistic studies. Tumor-derived extracellular vesicles (EVs) are implicated in pre-metastatic niche formation in other cancers. Here, we use immunocompetent models to define the stage at which SCC-derived EVs promote metastasis and identify their cellular/molecular targets.

Materials and methods: We established metastatic and non-metastatic murine SCC cell lines from spontaneous tumors in C57BL/6 mice with K15-Cre-driven Smad4 deletion and KrasG12D activation in the K15-positive keratinocyte stem cells. EVs were isolated via differential centrifugation, ultrafiltration, and size exclusion chromatography. Particle size and concentration were assessed by NTA, and morphology was confirmed by transmission electron microscopy. EV surface markers, including multi-pass transmembrane proteins, were analyzed using single-particle interferometric reflectance imaging. Proteomic analysis was conducted using DIA-MS at the UC Davis Proteomics Core. miRNA sequencing was conducted using the Illumina Novaseq 6000 at Novogene.

Results: Proteomic analysis indicated that EVs derived from metastatic SCC cells exhibit elevated integrins (ITGB1, $\alpha 2$, and $\alpha 3$) and chemokines (CXCL-1, 2, and 3) involved in cell motility and granulocyte chemotaxis compared to EVs from non-metastatic SCC cells. Exogenous introduction of metastatic EVs in tumor-bearing mice promoted tumor growth in vivo, and intratumoral injection of these EVs into ITGB1 KD tumors, which have reduced growth and metastatic capacity, improved growth and restored metastatic capacity. miRNA sequencing of EV cargo revealed enrichment for miRNAs with validated targets involved in growth/EMT regulatory pathways.

Summary/Conclusions: Our findings indicate that metastatic SCC-derived EVs promote tumor growth in ITGB1-intact recipient cells via paracrine/autocrine signaling and may compensate for ITGB1 loss in knockdown tumors through EV-associated ITGB1 and miRNAs targeting growth/EMT pathways.

61-A GALECTINS AS POTENTIAL TARGETS FOR HEPATOCELLULAR CARCINOMA (HCC) DIAGNOSIS AND THERAPY

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Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death. Its early detection and effective treatment options are limited. Novel approaches are urgently needed to target the molecular drivers of HCC and shut down pathological signaling. Several galactoside-binding lectins, namely galectins, have been shown to be overexpressed in HCC. Among these, galectin-1 has a high potential as a target for developing potential diagnostics and therapeutics. It induces epithelial-to-mesenchymal transition (EMT), facilitates tumor initiation and invasion, and promotes tumor growth. We have developed highly efficient chemoenzymatic strategies for synthesizing glycoside ligands for galectin-1. Immunology fluorescent imaging has been used to visualize the location of the galectins in human HCC cell lines. Selective galectin ligands have been identified using multiplex bead assays. They are being tested in cells engineered to express galectin-1 in different cell compartments for structure-function relationship studies and for the development of potential HCC biomarkers and therapeutics.

62-B SPATIAL TRANSCRIPTOMICS REVEALS DISTINCT ASCL1 AND ASCL2 GENE EXPRESSION PATTERNS IN ADVANCED PROSTATE CANCER

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Background: ASCL1 and ASCL2 are bHLH transcription factors reactivated in advanced prostate cancer. ASCL1 drives neuroendocrine differentiation and AR independence, while ASCL2 maintains stem-like programs and facilitates epithelial-to-neuroendocrine transition. Both promote lineage plasticity leading to castration-resistant and neuroendocrine prostate cancer (NEPC). This study examines their distinct expression patterns to elucidate lineage transitions and identify therapeutic targets.

Methods: Spatial transcriptomics was performed on a Gleason 10 specimen (10x Visium). ASCL1-high, ASCL2-high, and low regions were analyzed for differential expression and pathway enrichment (GSEA). A patient-derived xenograft (PDX) from the same patient was subjected to castration (intact n=4, relapsed n=6) and bulk RNA-seq. A cell line (UCDCaP) and its castration-resistant derivative (UCDCaP-CR) were established. Key genes were validated by qRT-PCR and Western blotting.

Results: ASCL1 and ASCL2 were mutually exclusive in patient tissues. ASCL1-high regions expressed higher WNT5A, FOLH1, INSM1, HES6, PEG10, PROX1 and lower AR, AKR1C3, MAOA, MET. GSEA showed E2F, Myc, DNA repair, neural lineage pathways in ASCL1-high regions; interferon, androgen response, EMT in ASCL2-high regions. Castration-relapsed PDX tumors showed increased AR, AKR1C3, CA9, ASCL1, ASCL2 and reduced FOXA1, ALDH1A3. UCDCaP-CR cells upregulated ASCL2 and neuroendocrine markers, downregulated ASCL1, PTEN, AR/P53 pathways.

Conclusions: ASCL1 and ASCL2 define distinct molecular states: ASCL1 linked to neural lineage/proliferation, ASCL2 to androgen response/EMT. Mutual exclusivity suggests divergent lineage plasticity. Transition toward ASCL2 dominance in castration-relapsed models with loss of AR/P53 signaling highlights their dynamic interplay in therapy resistance and neuroendocrine differentiation.

63-A RBM38 SENSITIZES TNBC CELLS TO FERROPTOSIS VIA REGULATION OF FTH1

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Triple-Negative Breast Cancer (TNBC) is an aggressive breast cancer subtype that lacks expression of estrogen receptor, progesterone receptor, and HER2, limiting targeted treatment options and contributing to poor clinical outcomes. Ferroptosis is a form of regulated cell death that is driven by lipid oxidation and iron-dependent accumulation of lipid peroxides. Interestingly, several studies have shown that TNBC cells rely heavily on elevated iron levels to drive rapid proliferation, tissue invasion, and metastasis, which may create an exploitable metabolic vulnerability. Here, we found that the RNA-binding protein RBM38 modulates ferroptosis in TNBC cells. Briefly, we found that loss of RBM38 sensitizes TNBC cells to several ferroptosis inducers, such as RSL3 and Erastin. We also found that loss of RBM38 leads to enhanced lipid peroxidation when stained by C11-BODIPY fluorescent probes. To uncover the underlying mechanism, we found that RBM38 is required for regulating the expression of FTH1 and FTL, both of which encode iron-storage proteins. Furthermore, we demonstrated that RBM38 represses the mRNA translation of FTH1 and FTL. Thus, ongoing studies are aimed at determining whether the RBM38-ferritin pathway can be therapeutically targeted for the treatment of TNBC using RBM38 inhibitors.

64-B INVESTIGATION OF C/EBP HOMOLOGOUS PROTEIN (CHOP) AS A FACILITATOR OF SARCOMA DEVELOPMENT

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High-grade complex karyotype sarcomas are a rare and heterogeneous group of tumors. Previously, we developed a model to study sarcoma development from human mesenchymal stem cells that accurately recapitulates the human disease. C/EBP homologous protein (CHOP) plays a key role in sarcoma, yet CHOP alone does not drive tumor formation. However, the addition of another oncogene with CHOP resulted in a more aggressive phenotype, indicating CHOP serves as a facilitator of sarcoma development. CHOP is a known downstream target of the Unfolded Protein Response (UPR), a pathway activated by endoplasmic reticulum stress. This preliminary study focuses on the role of CHOP in sarcoma development, specifically whether CHOP functions dependently or independently of the UPR to promote tumor formation. To determine if CHOP is functioning through the UPR, we used CRISPR-Cas9 to deplete the UPR's three branches: activating transcription factor 6 (ATF6), protein kinase R (PKR)-like kinase (PERK), and inositol-requiring enzyme 1a (IRE1a). We then performed an anchorage-independent growth assay to analyze transformation. We have previously demonstrated this assay is predictive of in vivo growth. To assess CHOP's function under oncogenic stress, we transduced our CHOP cell lines with a doxycycline-inducible YAP1 overexpression construct. Upon activation of YAP1, we conducted a Reactive Oxygen Species (ROS) assay to measure oxidative stress, a known driver of cellular transformation. At Day 14 of anchorage-independent growth, CHOP displayed no dependence on the ATF6 and IRE1a branches of the UPR for tumor transformation, as observed through colony count and size. Contrarily, CHOP was dependent on the PERK branch for transformation, suggesting utilization of this pathway when adapting to cellular stress. Finally, ROS levels increased in cells with activated YAP1 and CHOP compared to our control. Interestingly, our YAP1-CHOP overexpression decreased ROS levels, suggesting that in the presence of YAP1, CHOP can mediate cellular stress. We are currently working on identifying CHOP binding partners to determine non-UPR dependent mechanisms for sarcoma development. These findings further our understanding of the mechanism by which CHOP facilitates sarcoma development, establishing a more complicated pathway that highlights the PERK-CHOP axis as a potential therapeutic target for sarcomas.

65-A METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE AMONG ADOLESCENT AND YOUNG CANCER SURVIVORS

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Purpose: To evaluate the incidence of metabolic syndrome (MetS) and its association with cardiovascular disease (CVD) among adolescent and young adult (AYA; 15–39 years) cancer survivors.

Methods: We included 2-year survivors of 10 common cancers and a noncancer comparison cohort matched on age, sex, calendar year (2006–2020), and site from Kaiser Permanente Northern and Southern California. Participants were followed 2 years after diagnosis through 6/30/2023. MetS was defined as ≥ 3 of the following: diabetes, hypertension, obesity, high triglycerides, and low HDL cholesterol. We estimated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for MetS. Among cancer survivors, Cox models evaluated the association of MetS with incident CVD.

Results: AYA cancer survivors ($n=12,552$) had a 24% higher incidence of MetS than the comparison cohort ($n=112,130$; $IRR=1.24$; $CI, 1.18–1.31$). Incidence was higher for all MetS components, with the largest increase observed for diabetes ($IRR=2.43$; $CI, 2.29–2.59$). The highest IRRs for MetS were observed among survivors of acute lymphoblastic leukemia ($IRR=4.11$; $CI, 2.83–5.97$), acute myeloid leukemia ($IRR=2.45$; $CI, 1.67–3.59$), non-Hodgkin lymphoma (NHL; $IRR=1.66$; $CI, 1.36–2.02$), and Hodgkin lymphoma ($IRR=1.58$; $CI, 1.29–1.93$). Among survivors, MetS was associated with nearly twice the hazard of CVD ($HR=1.95$; 95% $CI, 1.56–2.44$), and this association was particularly pronounced among survivors of melanoma ($HR=3.17$; 95% $CI, 1.61–6.24$), cervical cancer ($HR=2.75$; 95% $CI, 1.00–7.53$), thyroid cancer ($HR=2.19$; 95% $CI, 1.26–3.83$), and NHL ($HR=2.13$; 95% $CI, 1.02–4.45$).

Conclusion: AYA cancer survivors experienced a higher incidence of MetS than those without cancer. The association between MetS and CVD underscores the need to incorporate metabolic screening and early management of modifiable risk factors into survivorship care.

66-B BREAKING BARRIERS TO BREAST CANCER SURVIVORSHIP CLINIC

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The five-year overall survival of breast cancer in the United States is approaching 93% and the ten-year survival is nearing 87%. This widens an essential care gap and underscores the growing importance of providing comprehensive support services to breast cancer survivors. Though this concept itself is not novel, such models remain underutilized. To assess survivorship service utilization at UC Davis, this study examined the perspectives of breast cancer providers referring patients to the UC Davis Breast Cancer Survivorship Clinic. This clinic began serving patients on March 13, 2025, and over a nine month period had provided care to 45 survivors. The relatively low referral rate prompted the development of a survey to better understand providers' perspectives regarding referral to the survivorship clinic.

The most common referral trigger was sexual or fertility dysfunction, followed by patient-initiated requests and psychosocial distress. However, only 67% of respondents strongly agreed that they were able to identify when a patient should be referred to the survivorship clinic. Similarly, only 50% strongly agreed that they were confident in explaining the purpose of the survivorship clinic to their patients. Despite their individual understanding, 83% expressed interest in learning more about the survivorship clinic. This survey was limited by its small sample size ($n=6$); however, it highlighted several important barriers to referring patients to the survivorship clinic.

It is essential to optimize the utilization of survivorship clinics, as existing literature demonstrates that these clinics can improve adherence to recommended surveillance and maintenance endocrine therapy, ultimately contributing to improved outcomes among breast cancer patients. Based on the survey findings, targeted interventions were developed to improve referral rates to the UC Davis survivorship clinic. An EMR SmartPhrase was developed and will be shared with breast cancer providers to facilitate identification of patients appropriate for survivorship clinic referral. This SmartPhrase incorporates prompts to assess key areas of survivorship and when closer follow-up is indicated it recommends referral to the survivorship clinic. As a next step, an EMR Practice Advisory will be developed to further streamline the referral process by automatically prompting providers to refer patients who meet predefined criteria.

67-A CIRCADIAN GENE VARIANTS AND BREAST CANCER RISK IN PERUVIAN WOMEN

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Background: Breast cancer susceptibility results from the interaction between inherited genetic variation and environmental factors. The circadian rhythm regulates cellular processes to maintain genomic and metabolic homeostasis. Germline variants tagging genes implicated in the circadian rhythm may influence circadian regulation and modify breast cancer risk. We aimed to explore the association between common germline variants in circadian rhythm genes and breast cancer risk in Peruvian women and to prioritize candidate loci for further investigation in other Latin American populations.

Materials and Methods: We analyzed genetic data from 1,809 breast cancer patients recruited at the INEN through the PEGEN-BC study in Lima Peru, and 3,339 cancer-free women from a pregnancy study in Lima. Individual-level genotype data were processed through a harmonized quality-control pipeline and imputed to TOPMed ($r^2@1.0.0$). Using PLINK v1.9, we evaluated the impact of 3,702 variants across

14 circadian-related genes on breast cancer risk. The models were adjusted for the first ten principal components to control for population structure. A Benjamini–Hochberg false discovery rate (FDR) ≤ 0.05 was considered suggestive.

Results: Among 3,702 variants, 211 showed suggestive associations with breast cancer risk (FDR < 0.01). The top associated variants included rs75307902 in the PER3 gene (locus 1p36.23, odds ratio (OR) = 0.58, 95% CI: 0.41–0.80), rs34509802 in the NPAS2 gene (locus 2q11.2, OR = 1.45, 95% CI: 1.15–1.84), rs11071588 in the RORA gene (locus 15q22.2, OR = 0.88, 95% CI: 0.80–0.95), and rs1410226 in the RORB gene (9q21.13, OR = 0.85, 95% CI: 0.75–0.95).

Conclusion: The observed signals in the PER3, NPAS2, RORA, and RORB genes, might affect breast cancer risk through cellular growth and microenvironment regulation. Candidate variants will be tested for independent replication and functional annotation. These findings represent an initial step towards understanding the relationship between circadian rhythm regulation and breast cancer susceptibility in Peruvian women, an underrepresented population in genomic research.

68-B MEETING PEOPLE WHERE THEY ARE: AN EQUITY-FOCUSED TOBACCO CESSATION STRATEGY FOR CANCER PREVENTION IN TINY-HOME COMMUNITIES

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Background: Tobacco use remains a leading preventable cause of cancer morbidity and mortality. Adults experiencing housing instability face disproportionately high tobacco use with environmental exposures associated with cancer. (i.e.sun). Substantial barriers exist to accessing tobacco cessation treatment and cancer screenings. This ongoing feasibility study examines tobacco-use patterns, cessation experiences, facilitators and barriers to cessation, and preferred support strategies used in adults living in tiny-home communities. This study will inform future projects for creating accessible, community-based cancer-prevention interventions.

Methods: Adult residents of tiny-home communities were recruited through a nurse-led mobile clinic. Participants completed a questionnaire assessing nicotine products used, indicators of nicotine dependence, previous quit attempts, tobacco-use triggers, healthcare utilization, openness to cessation and wellness support, and preferred support approaches. We sought to identify key barriers and facilitators to tobacco treatment. The intervention for this model integrates tobacco-use assessment, brief counseling, treatment support, and referral to cessation resources. Preliminary questionnaire data collected through July 24, 2026, were analyzed using descriptive statistics.

Results: Fifty-two participants completed the questionnaire. Cigarette use was reported by 49 participants (94.2%), while 22 (42.3%) reported nicotine vaping; participants could select multiple products. Among 50 participants responding to the dependence-timing question, 46 (92.0%) reported nicotine use within 30 minutes of waking. Thirty-five participants (67.3%) had previously attempted to quit or reduce their tobacco use. Stress or emotional upset was the most frequently reported trigger (75.0%), followed by boredom (55.8%). Nearly all participants (98.1%) were at least somewhat open to receiving wellness or tobacco-use support, including 59.6% who were very open. Preferred approaches included phone or text support (46.2%) and one-on-one, in-the-moment assistance (32.7%). Twenty-two participants (42.3%) reported an emergency department visit within the previous six months.

Conclusions: Preliminary findings demonstrate substantial nicotine dependence alongside strong openness to community-based support from trusted-known health care providers. Interventions that address stress and boredom while providing flexible, immediate, and mobile-accessible services may improve engagement in tobacco cessation among residents of tiny-home communities. Continued enrollment and implementation evaluation will inform the feasibility and design of a larger equity based community focused cancer-prevention intervention.

69-A PROSPECTIVE EVALUATION OF A THIRD-PARTY HIPAA-COMPLIANT PHYSICIAN-SPECIFIC PATIENT EDUCATION WEBSITE IN A UROLOGIC ONCOLOGY PRACTICE

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Objectives: To evaluate the feasibility and patient-perceived value of WellPrept, a HIPAA-compliant, physician-tailored digital education platform, delivered to new urologic oncology patients prior to their initial consultation as part of a PDSA quality improvement initiative.

Methods: New urologic oncology patients of a single provider received a link to the WellPrept platform via MyChart, email, and/or text messaging before their first visit. Patients of partner providers served as a comparison group and did not receive pre-visit education. The study accrual period was 3 months. All new patients completed a survey at their first visit assessing recall, engagement, and perceived educational value. Information source utilization was compared between groups using chi-square tests.

Results: Of 137 patients approached, 136 (99%) consented. The population was predominantly male (92%), aged ≥ 60 (80%), with 96% smartphone access. Forty-eight patients (35%) recalled receiving WellPrept. Among 46 intervention respondents, 100% found the platform accessible, 96% rated it as organized, and 80% viewed at least half the content. Key outcomes: 100% reported improved understanding of their urologic condition, 98% felt more prepared to ask questions, 91% better understood what to expect at their first visit, 85% reported reduced pre-visit anxiety, 98% endorsed that materials supported shared decision-making, and 98% would recommend the platform to other patients. Among 87 comparison respondents, 93% would have reviewed materials if provided, 92% believed they would have been helpful, 85% felt they would have reduced anxiety, and 93% wanted similar materials before future specialist visits. Recipients were significantly more likely to use hospital/clinical websites (66% vs. 40%, $p=0.009$) and less likely to use forums/social media (18% vs. 40%, $p=0.021$) or friends/family (18% vs. 42%, $p=0.011$).

Conclusions: WellPrept demonstrated strong feasibility and high patient-perceived value as a pre-visit educational tool in urologic oncology. Near-universal positive outcomes among recipients, combined with robust demand from non-recipients and a significant shift toward more reliable information sources, support expanding the platform to additional providers and specialties. These findings inform the next PDSA cycle, which will focus on multi-channel delivery strategies to improve the 35% recall rate.

70-B HOW MUCH OF CANCER MORTALITY SOCIOECONOMIC INEQUITIES MIGHT SMOKING CAUSE? CURRENT LUNG/NON-LUNG CANCER MORTALITY RATE ASSOCIATIONS ACROSS EDUCATION STRATA IN U.S. MEN and WOMEN

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Background. Tobacco industry and health leaders substantially concurred that tobacco sales are sustained by camouflaging. So usual cohort study convenience/volunteer “smoker” missamplings that deflate tobacco toll estimates and inflate tolls “adjusted for smoking,” help sustain smoking tolls. So, we instead accounted for both all smokers and all smoking, and quantified U.S. smoke load (cumulative smoking damage) (cancer age-standardized mortality rate (ASMR) associations across education strata, by gender .

Methods: We used: newly reported cancer.org 2019-2023 cancer ASMRs for ages 25-74. We used lung cancer ASMRs as a smoke load bio-index and ran lung/non-lung (all sites minus lung) cancer ASMR regressions, by gender.

Results: Tight lung/non-lung cancer ASMR associations were seen across education strata for men ($R^2=0.99$, slope=1.85 (95% confidence interval (CI): 1.23-2.46), $p=0.02$) and women ($R^2=0.98$, slope=1.83 (CI -1.06–4.73), $p=0.08$).

Discussion: Both recent U.S. men and women non-lung cancer ASMRs correlate nearly perfectly with their smoke loads across education strata ($R^2=0.99$, $p=0.02$ for males and, albeit $p=0.08$, $R^2=0.98$ for females). So smoke load variation can explain 50-99 times the residual non-lung cancer ASMR variance explained by all other factors combined. This supports past findings of near perfect national time series lung/non-lung cancer ASMRs associations in many nations and new Harvard findings that smoking drove costly (\$40 trillion), increasing middle age total mortality excesses in U.S. rural and less educated populations. Those reversed their 1990s mortality deficits.

Cancer.org says that such ASMR inequities are due to social determinants of health of cancer victims. That may be a smokescreen, obscuring smoking effects and blaming victim attributes. Instead, this and prior tight lung/non-lung cancer ASMR associations show smoke exposure is a near sole and remediable driver of cancer mortality inequities as Harvard researchers noted for 1990-2020.

This is a recent U.S. cancer education/population level association, Studying smoking effects in other fatalities, nations, genders, inequities,... is warranted. Focusing on tobacco control as the near sole way to reduce U.S. education-linked cancer ASMR inequities is warranted.

71-A A LOCAL LENS FOR CANCER SCREENING NEEDS ASSESSMENT: OAK PARK, SACRAMENTO

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The demographic characteristics and healthcare outcomes of the Oak Park community in Sacramento County, California, were assessed focusing on cancer screening and prevention. Guided by the socio-ecological framework, the analysis examined individual, social, community, and structural factors associated with health outcomes across five U.S. Census tracts (27, 28, 37, 44.01, and 44.02) within the Florin/Fruitridge/Oak Park/Parkway/South Sacramento Medical Service Study Area. Data from the CDC PLACES Project, Behavioral Risk Factor Surveillance System (BRFSS), the 2020 U.S. Census, and the American Community Survey were obtained through the UCSF Health Atlas, an interactive online mapping tool. Data from the Sacramento County's Community Health Improvement Plan (CHIP), a tool that integrates 23 community characteristics, including social determinants of health such as education, economic, and housing conditions into a Healthy Places Index (HPI), was also explored.

Based on CHIP data, all census tracts in Oak Park fall below the county-wide average HPI score, and census tract 44.01 has the lowest HPI score out of the entire county. Screening rates for breast, cervical, and colorectal cancers in the five Oak Park census tracts were compared to Sacramento County and national averages. Census tracts 37 and 44.02 consistently demonstrated lower screening rates. Mammography screening ranged from 67.0% to 68.8% in the lowest-performing tracts, compared with the county average of 71.7%. Cervical cancer screening was lowest in tract 44.02 (73.8%) versus county and national averages of approximately 81.8%. Colorectal cancer screening indicated the largest disparity, with tract 44.02 reporting only 46.3%, substantially below the county (61.1%) and national (65.0%) averages. The reported prevalence of non-skin cancers was below county and national estimates across all Oak Park tracts.

The reported findings likely reflect underdiagnosis associated with lower screening uptake, rather than a lower disease burden, and highlight cancer screening disparities affecting the population of Oak Park. Community-based interventions are needed to improve access and use of cancer screening tools and other preventative care, ultimately reducing the burden of disease and improving quality of life in Oak Park.

72-B IMPLEMENTING TARGETED HUMAN PAPILLOMAVIRUS (HPV) VACCINE EDUCATION IN COLLEGE-AGED CATCH-UP POPULATIONS AT UC DAVIS

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Introduction: Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States and a cause of cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancer. Although HPV vaccination can prevent > 90% of cancers caused by HPV, college-aged individuals, who fall in the catch-up population (ages 18-26) have the lowest vaccination rates amongst eligible age groups. Previous studies amongst college students identified low HPV health literacy involving misconceptions regarding HPV transmission, vaccine eligibility and HPV-caused cancer as a barrier to informed decision-making and vaccine uptake.

Methods: We developed and delivered a one-hour, Powerpoint-based educational HPV vaccine intervention in classroom settings. During the sessions, students learned about HPV transmission, risk, associated cancers, and prevention. Through interactive scenarios, students practiced how they would educate community members by responding to common HPV misconceptions and vaccine hesitancy, addressing stigma, and advocating for HPV vaccination as cancer prevention. We recruited participants through student organizations, campus-based

organizations, and tabling. We evaluated the effectiveness of the intervention with an eight-question questionnaire delivered before and after the educational session. Responses were scored as correct (1) or incorrect (0). We computed question-specific scores as the percentage of participants that correctly answered each question, and a global knowledge score with the mean value of all correctly answered questions. We evaluated differences in global knowledge score with paired t-tests.

Results: As of August 14, 2026, we have conducted 16 sessions, with 434 student participants. Question-specific scores improved in all questions, with the largest increases in understanding HPV transmission (20.7% to 74.3%), HPV risk (46.3% to 90.1%), and identifying HPV-associated cancers (23.9% to 89.5%). Global knowledge scores increased from 4.5 (SD=1.36) pre-intervention to 7.15 (SD=0.89) post-intervention, with a mean improvement of 2.62 points (95% CI: 2.38-2.87; $p < 0.001$) and a large effect size (Cohen's $d = 1.67$).

Conclusions: These findings suggest that targeted HPV education can substantially improve HPV health literacy among college students. Future evaluation will use a 3-month follow-up survey to assess changes in HPV vaccine attitudes, HPV-associated cancer screening behaviors, and information dissemination.

73-A DISPARITIES IN MELANOMA SURVIVAL ACROSS RACIAL AND ETHNIC GROUPS IN RURAL AND URBAN COMMUNITIES

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Melanoma is among the deadliest skin cancers, yet it is often curable with timely treatment. Racial and ethnic disparities in melanoma survival are well documented, but survival by residence remains underexplored. Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry, we identified 393,058 patients diagnosed with a first primary cutaneous melanoma during 2004–2022 with known race and ethnicity; 38,611 (9.8%) died of melanoma (median follow-up = 102 months). We used Cox proportional hazards models to examine the association of rurality, race and ethnicity, and household income with melanoma-specific survival, controlling for stage at diagnosis, age, sex, anatomic site, Breslow thickness, and initial treatment type; results are presented as adjusted hazard ratios (HR). Rural residence was not associated with melanoma-specific survival (HR 1.02, 95% CI 0.98–1.05), and there was no evidence of an interaction between rurality and race and ethnicity ($p = 0.38$). Race and ethnicity violated the proportional-hazards assumption ($p < 0.001$), so HRs were estimated within 0–12 and greater than 12 months from diagnosis. Racial and ethnic disparities were substantial and widened beyond the first year after diagnosis. After 12 months, non-Hispanic Black (HR 1.63, 95% CI 1.46–1.83), non-Hispanic Asian/Pacific Islander (HR 1.54, 1.38–1.73), Hispanic (HR 1.29, 1.22–1.36), and non-Hispanic American Indian/Alaska Native (HR 1.28, 1.03–1.58) patients experienced an increased hazard of melanoma-specific death compared to non-Hispanic White patients. In the first 12 months, differences were smaller: non-Hispanic Black (HR 1.19, 95% CI 1.03–1.37), non-Hispanic Asian/Pacific Islander (HR 1.14, 0.98–1.34), Hispanic (HR 1.06, 0.99–1.14), and non-Hispanic American Indian/Alaska Native (HR 0.89; 0.61–1.29). The hazard of melanoma-specific death rose steadily with decreasing income (HR 1.61, 95% CI 1.43–1.80; lowest versus highest income stratum). These findings suggest that racial, ethnic and income disparities, rather than rurality, drive differences in melanoma-specific survival. Racial and ethnic disparities widened after one year, consistent with reports in other cancers where racial disparities emerge or persist after initial treatment, suggesting a role for differences in follow-up care, recurrence surveillance, and access to effective therapies at relapse.

74-B ENROLLING PARTICIPANTS INTO THE ASIAN AMERICAN PROSPECTIVE RESEARCH COHORT (ASPIRE) AT UC DAVIS

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Asian Americans comprise people who originate from Asia, the largest and most culturally heterogeneous continent, including more than 30 national entities, and speaking more than 200 languages or dialects. Until 2024, no cohort study had been launched to understand the diverse etiologies of cancer occurrence in Asian Americans, the first US racial/ethnic population to experience cancer as the leading cause of death and the population with the highest growth rate of any US population. In 2024, ASPIRE was launched as the first NCI-funded national cohort to longitudinally elucidate the cancer etiology of Asian Americans. Any Asian American who resides in the US, ages 40-75, without cancer is eligible. Led by UCSF, the scope of this study is to enroll 20,000 Asian Americans nationwide, with focused community-based recruitment efforts in CA, NJ, NY, and PA. While all sites aim to recruit Asian Americans across all ethnicities, the UCD ASPIRE recruitment effort distinctly focuses on Hmong and Vietnamese through bilingual/bicultural outreach.

We concentrated our efforts on these populations because ASPIRE institutions elsewhere had more limited capacity to focus on these populations. In fact, Sacramento has one of the largest concentrations of Hmong and Mien in the US. Filipino and Vietnamese were populations we had worked with previously. This poster describes the implementation of the UCD ASPIRE's research outreach infrastructure, community engagement approaches, and the motivations that are propelling data collection to address the research data gaps especially in Filipino, Hmong, Mien, and Vietnamese American populations. Building on previous community experiences and in accordance with the Indigenous Model, only ethnically-specific bilingual/bicultural recruiters were hired; they were certified in human subjects research protection and trained in recruitment approaches.

The ASPIRE team at UCD includes faculty, students, health professionals, and community leaders. This built-in mix makes respect for all cultures central, encourages interdependent collaborations, and facilitates outreach through networking and webinars, tabling at community events, places of worship, and reaching people in sporting events. The most important driving force for ASPIRE is the inspiration that participating through furnishing individuals' data will contribute towards increasing enhanced health data for Filipino, Hmong, Mien, and Vietnamese.

75-A IS THERE A DIFFERENCE IN WHO IS OFFERED FERTILITY SPARING TREATMENT IN PATIENTS WITH EARLY-STAGE GYNECOLOGIC CANCERS?

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Introduction: This study investigates if there are demographic differences in patients with early-stage gynecologic cancers being offered fertility sparing treatment (FST).

Methods: This is a single institution, retrospective cohort study including patients 18-40 years old with a diagnosis of early stage ovarian, endometrial, or cervical cancer or ovarian borderline tumor. Demographics and documented treatment recommendations were collected to determine if patient characteristics (race, ethnicity, or age) influenced FST offer rates. Pregnancy and oncologic outcomes were also assessed.

Results: Of 131 FST-eligible patients, 82.4% were offered FST and 69.4% underwent FST. FST offer rates showed no difference by race (white (82.3%) vs non-white (82.6%) $p=0.96$) or ethnicity (Not Hispanic or Latino (79.3%) vs Hispanic or Latino (88.9%) vs other/unknown (87.5%) $p=0.41$). However, offer rates decreased as age increases. Rates of FST offered declined in older patients with patients under 30-years-old more likely to be offered FST than those over 30-years-old (97.1% vs. 77.3%, $p=0.0080$). Of those who accepted FST treatment and received follow up care, 17.3% ultimately underwent definitive cancer treatment, and 25.5% had a reported live birth after or during treatment.

Conclusion/Implications: Older patients (greater than 30 years old) were less likely to be offered FST as a cancer treatment option. This suggests potential clinician implicit bias in FST treatment recommendations. Further studies are needed to address how clinicians are counseling child-bearing age patients with early-stage gynecologic cancers eligible for FST.

76-B GERMLINE GENETICS OF CHRONIC INFLAMMATION AND BREAST CANCER RISK IN PERU: BUILDING POPULATION-SPECIFIC RESOURCES FOR TARGETED CANCER PREVENTION IN LATIN AMERICA

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Introduction: Breast cancer is the leading cause of cancer-related mortality among women in low- and middle-income countries, including Peru. Chronic inflammation is involved in DNA damage, tumor initiation, and cell proliferation. Nevertheless, the contribution of inherited variation in genes involved in inflammatory pathways to breast cancer susceptibility remains poorly understood, particularly in underrepresented Latin American populations. We therefore investigated whether germline variants tagging genes involved in immune and inflammatory pathways are associated with breast cancer risk in Peruvian women.

Methods: Breast cancer patients were recruited through the Peruvian Genetics and Genomics of Breast Cancer Study (PEGEN-BC; N = 1,809) at the Instituto Nacional de Enfermedades Neoplásicas (Lima, Peru). Women without breast cancer from a pregnancy outcomes study conducted in Lima were included as convenience controls (N = 3,339). Genome-wide genotype data were imputed using the Michigan Imputation Server (TOPMed), followed by standard quality control. Breast cancer risk was evaluated using logistic regression models adjusted for the first ten principal components. We performed a targeted analysis of variants within ± 250 kb of 12 genes involved in immune and inflammatory pathways, namely IL6, IL6R, IL1B, TNF, TGFB1, IL10, PTGS2, CXCL12, CCR5, TLR4, CRP, and NFKB1. Bonferroni correction was applied for multiple testing.

Results: A total of 20,528 variants were evaluated. Although no variant reached the significance threshold ($P_{\text{Bonferroni}} < 2.44 \times 10^{-6}$), 20 variants demonstrated suggestive associations ($P_{\text{Bonferroni}} \leq 9.40 \times 10^{-4}$), mapping to CRP, CXCL12, PTGS2, and NFKB1. Seventeen (85%) of the variants with a suggestive association clustered to chromosome 1, including 13 (65%) mapping to CRP and 4 (20%) mapping to PTGS2. These genes encode C-reactive protein, a key biomarker of systemic inflammation, and prostaglandin-endoperoxide synthase 2 (PTGS2/COX2), an enzyme involved in the inflammatory response. Moreover, rs4074024, an intron variant in CRP, showed the strongest association (OR= 1.92; 95% CI: 1.39-2.67; $P_{\text{Bonferroni}} = 9.40 \times 10^{-5}$).

Conclusion: Our findings suggest that germline variation in key genes involved in immune and inflammatory pathways may contribute to breast cancer risk among Peruvian women. Validation in larger cohorts, subtype-specific analyses, and integration of these variants into polygenic risk models may improve targeted prevention strategies in this and other Latin American populations.

77-A CHARACTERIZATION OF PERCEIVED AND MEASURED ENVIRONMENTAL CANCER RISK FACTORS: FINDINGS FROM THE UC DAVIS COMPREHENSIVE CANCER CENTER CATCHMENT AREA POPULATION ASSESSMENT

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Introduction: Individual perceptions of environmental cancer risk are shaped by place-based factors (e.g., particulate matter levels where one lives) and individual-level factors (e.g., culture, and education). However, the joint assessment of place-based and individual-level factors with perceived cancer risk remains poorly understood. To characterize these relationships, we leveraged data from the UC Davis Comprehensive Cancer Center (UCDCCC) catchment area population assessment (CAPA) survey.

Methods: The CAPA survey is a cross-sectional, address-based assessment of adult residents from the 19-county UCDCCC catchment area. We coded responses to identify individual-level concerns for cancer risk as it related to wildfire smoke, industrial air pollution, water pollution, and agriculture. We linked survey respondent locations to census tract-level geospatial environmental data from CalEnviroScreen 4.0 (CES 4.0) and the UC Davis Air Quality Research Center to estimate mean annual concentrations for environmental pollutants. Using

separate univariate and multivariable models for each environmental concern, we modeled concern vs not concerned against geospatial data and individual-level data to determine which factors influence cancer risk perceptions in our catchment area. Significance was defined as two-sided p-value < 0.05.

Results: Among 2,007 respondents, most were ≥60 years old (64.4%), female (66.9%), had the lowest SES (38%), lived in urban communities (82.3%) and had no previous personal history of cancer (74.8%). Wildfire smoke (62%), air pollution impacting water safety (42%), and industrial air pollution (41%) were the most frequently reported environmental concerns. Participants concerned about wildfire smoke lived in census tracts, that on average, had higher biomass-derived PM_{2.5} (p = 0.008), whereas those concerned about industrial air pollution resided in census tracts, that on average, had higher non-biomass derived PM_{2.5} (p = 0.003). Rural residents were less likely to report concerns about industrial air pollution, air pollution affecting food safety, and water safety (all p < 0.05), but were 54% more likely to report concerns about wildfire smoke (OR=1.54; 95% CI=1.20–1.98).

Conclusion: This work suggests a concordance between perceived environmental concerns and both individual-level and place-based factors. Understanding community perceptions about their vulnerability to environmental cancer hazards can help public health practitioners to target and prioritize community activities, policy needs, and communication strategies.

78-B UROTEPATI: PROSTATE CANCER SCREENING AWARENESS AND EDUCATIONAL NEEDS AMONG PATIENTS AT A STUDENT-RUN FREE CLINIC SERVING LATINO COMMUNITIES

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Background: Disparities persist in prostate cancer screening and education among Latino men, contributing to later-stage diagnoses and higher mortality. This study evaluates baseline screening interest, health literacy regarding screening procedures, and history of patient-provider communication among underserved Latino patients at Clínica Tepati, a student-run free clinic (SRFC) in Sacramento, California.

Methods: We conducted an ongoing, cross-sectional, language-concordant survey of Clínica Tepati patients beginning in March 2026. The survey assessed prostate status, prior prostate cancer discussions and screening, screening knowledge, perceived barriers, comfort discussing prostate cancer, interest in screening, and preferred educational supports. Deidentified responses were collected in Qualtrics and analyzed descriptively in Excel. Item-level denominators varied due to skip logic and partial responses. The study was deemed IRB-exempt.

Results: Among 50 completed surveys, 16 respondents (32%) reported having a prostate, most of whom were >40 years old (13/16, 81%). Among respondents completing prostate cancer screening items (n=12), most had never discussed prostate cancer with a provider (8/12, 67%) or undergone prior prostate cancer screening (8/12, 67%). Despite this, most reported comfort discussing prostate cancer (10/12, 83%) and interest in screening (10/12, 83%). Knowledge gaps were common: 79% (11/14) did not know or were unsure that family history increases prostate cancer risk, and 79% (11/14) did not know or were unsure how cancer screening is performed. Common perceived barriers to screening included cost (6/11, 54.5%) and lack of insurance (5/11, 45.5%). Talking with a doctor was the preferred method for receiving prostate cancer education (12/14, 86%).

Conclusions: Preliminary findings suggest a gap between prostate cancer screening interest and prior screening experience among Clínica Tepati patients completing prostate-specific survey items. Despite low rates of prior provider discussion and screening, respondents reported high comfort discussing prostate cancer and strong interest in screening. Knowledge gaps regarding risk factors and the screening process, alongside cost and insurance barriers, support the role of student-run free clinics in providing prostate cancer education, screening counseling, and navigation to low-cost care.

79-A GENETIC ANCESTRY SHAPES BOTH PATHOGENIC VARIANT DETECTION AND VARIANT INTERPRETATION IN PERUVIAN WOMEN WITH BREAST CANCER

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Breast cancer genetic testing may guide risk-reduction and early detection for healthy women and treatment for patients with breast cancer. However, most existing evidence derives from populations of predominantly European ancestry. In this study, we investigated how genetic ancestry influences both the detection of known pathogenic/likely pathogenic (P/LP) variants and the interpretation of variants of uncertain significance (VUS) among Peruvian women with breast cancer, a population characterized by higher Indigenous American ancestry.

Targeted germline gene sequencing on 11 high- and moderate-penetrance breast cancer susceptibility genes was performed in 1,359 women with breast cancer from Lima, Peru. P/LP variants were identified in 104 (7.65%) patients. The genes with the highest prevalence of P/LP variants were BRCA1 (1.77%), BRCA2 (1.47%), ATM (1.47%), PALB2 (1.18%), and CHEK2 (0.96%). Compared to patients without P/LP variants, P/LP variant carriers were more likely to have a first-degree family history of breast cancer (p < 0.001), to be diagnosed at a younger age (p = 0.007), to present with poorly differentiated or undifferentiated tumors (p < 0.001), and to have triple-negative breast cancer (p = 0.003). An enrichment of European local ancestry at the BRCA1 P/LP variant locus in carriers was observed compared to non-carriers, suggesting a gap in available knowledge about the P/LP status of variants within non-European chromosomal segments in the BRCA1.

We also evaluated the predicted reclassification of VUS using five in silico prediction tools, including AlphaMissense, ESM-1b, REVEL, VARIITY, and CADD. Among 138 distinct VUS, 13.8% were predicted to be pathogenic and 57.2% benign. Predicted pathogenic variants were enriched among individuals with higher European ancestry, whereas predicted benign variants were more common among those with higher Indigenous American ancestry. These ancestry related patterns were observed in AlphaMissense, ESM-1b, REVEL, and VARIITY, whereas CADD showed no detectable association between predicted variant deleteriousness and ancestry proportions. Our findings

suggest that in silico prediction of VUS in Peruvian women with breast cancer may be influenced by genetic ancestry.

These findings highlight the importance of including diverse populations in genetic studies to uncover population-specific risk alleles that may be missed in predominantly European-based research.

80-B “WHAT’S IN IT FOR ME”: COMMUNITY-GUIDED ADAPTATION OF BREAST HEALTH EDUCATION AND TEXT MESSAGING FOR MOBILE MAMMOGRAPHY

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Background: Mobile mammography can reduce structural barriers to breast cancer screening, but its impact may be limited by screening-related fears, misconceptions, health-literacy needs, and insufficient culturally relevant education. Increasing participation requires both accessible screening services and education that addresses these barriers. Incorporating community perspectives can ensure that messaging is understandable, acceptable, and responsive to medically underserved populations while increasing awareness, addressing concerns, and encouraging participation in mobile mammography.

Aim: To obtain community feedback to refine UC Davis mobile mammography educational materials and develop culturally relevant, supportive text messages addressing appointment preparation, reminders, and barriers to screening.

Methods: Three approximately one-hour focus groups were conducted with 26 adult community members from City Church Sacramento. Participants reviewed a breast health education slide deck and eight text messages: three pre-appointment messages, three appointment reminders, and two addressing screening barriers. They provided feedback on the slide deck, selected preferred messages, and discussed message content, tone, timing, and frequency, as well as the presentation’s clarity, delivery, and motivational value. Data were analyzed using a rapid qualitative approach guided by the PEARL framework: Plain Language, Explicit Data, Affirmative Framing, Representative Content, and Local Connection.

Results: Five themes aligned with the PEARL framework.

P: Participants preferred brief, direct messages prioritizing appointment details and recommended clarifying the presentation’s purpose, graphics, and screening duration. E: For text messages, participants preferred flexible screening-duration estimates to support planning and reduce anxiety. For the presentation, they requested information on racial disparities, risk and protective factors, and asymptomatic breast cancer. A: Participants preferred empowering language emphasizing screening benefits and team support. R: Participants recommended real-life images representing women of color and other populations served, while acknowledging that men can also develop breast cancer. L: Messages should reflect practical access needs and daily routines. Most participants preferred two reminders—approximately one week and one day before the appointment or the morning of—with early-morning delivery commonly favored. A walkthrough video was recommended to familiarize first-time patients with mobile mammography.

Discussion: Community feedback will guide the adaptation of the educational materials to ensure they are clear, supportive, culturally relevant, and responsive to practical screening barriers.

81-A INTEGRATING NON-TARGETED CHEMICAL ANALYSIS WITH SPATIAL FUEL AND STRUCTURAL DAMAGE DATA TO ASSESS FIREFIGHTER EXPOSURES IN SOUTHERN CALIFORNIA WILDFIRES IN 2024-2025

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Background: California’s firefighters (CA-FFs) face heavy occupational exposures due to the increasing frequency and severity of wildland-urban interface (WUI) fires. The precise mixture of chemicals at the fire front, and the resulting health impacts, remains poorly understood. To comprehensively assess these risks and address the data gap regarding complex mixtures of toxicants, this study moves beyond standard targeted chemical lists to characterize the environment in which CA-FFs operate.

Methods: In a collaboration between the Los Angeles County Fire Department and University of California researchers, exposures were monitored during five major fires (Line, Bridge, Franklin, Eaton, and Palisades) between September 2024 and January 2025. Sampling utilized stationary sorbent tubes at engine locations, silicone wristbands worn during field operations, and post-shift skin wipes. Gas chromatography-quadrupole time-of-flight mass spectrometry (GC-QTOF-MS) identified and assessed relative abundances of chemicals on wristbands and wipes. Sorbent tubes quantified volatile and semivolatile organic compounds via unit resolution GC-MS. To contextualize exposures, we integrated CAL FIRE Damage Inspection Program (DINS) data evaluating structural damage and LANDFIRE fuel model data characterizing vegetative fuel loads within fire perimeters.

Results: Silicone wristbands yielded more comprehensive chemical exposure profiles than skin wipes. Untargeted GC-QTOF-MS analysis isolated 1,467 features that passed initial blank and noise filters, with an automated algorithm annotating 424 features at high confidence. Although experimental carcinogenicity data is lacking for many structures, quantitative structure-activity relationship (QSAR) modeling within the VEGA platform predicted 76 compounds to be carcinogenic with “good reliability”. These exposure profiles are currently being evaluated against spatial DINS and LANDFIRE data to establish relationships between fuel models, structural impacts, and predicted carcinogens at the fire front.

Conclusions: Coupling non-targeted chemical exposure characterizations with spatial fuel and structural damage data expands our understanding of toxic WUI fire exposures. This comprehensive approach provides critical insights necessary to inform risk assessments and develop preventative interventions protecting the health and resiliency of the fire service workforce.

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