Ralph de Vere White
Symposium for Early Stage
Investigators in Cancer

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Oral Presentations

1 GD2-TARGETED DELIVERY OF BIORNA FOR HIGH-RISK NEUROBLASTOMA THERAPY USING REDOX-RESPONSIVE POLYMER NANOPARTICLES

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

Method: Low molecular weight (LMW) PEI (1.2 kDa) was thiolated and cross-linked via disulfide bonds to impart redox-responsiveness. The resulting polymer was modified with PEG (2 kDa) and 3-aminophenylboronic acid (PBA) to target GD2 gangliosides. PBA-PNPs were formed by complexing the carrier with miRs and 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, ensuring colloidal stability. 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 1.90-fold increase in cellular uptake compared to non-targeted PNPs, suggesting GD2-mediated delivery. Notably, our platform maintained high cell viability (~100%), demonstrating minimal carrier-related toxicity compared to standard delivery systems. When loaded with tumor-suppressive miRs, PBA-PNPs exhibited increased HRNB cell killing compared to non-targeted controls. In vivo studies using an HRNB mouse model showed 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.

Lay Language Abstract: High-risk neuroblastoma is a pediatric cancer that is difficult to treat with current medical approaches. Our research introduces a delivery system that uses a targeting mechanism to reach cancer cells directly. Once inside the tumor, the carrier releases miRNA in response to the specific chemical environment of the cancer. This method aims to enhance the precision of the treatment by focusing it on tumor cells, which may help minimize unintended effects on healthy parts of the body.

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2 SYNERGISTIC IN VIVO THERAPY USING BIOENGINEERED MICRORNA AND CHEMOTHERAPY FOR HIGH-RISK NEUROBLASTOMA

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Introduction: High-risk neuroblastoma (HRNB) is a common pediatric cancer with a survival rate of 50% despite intensive therapy. In this study, we evaluated a novel strategy combining bioengineered microRNA (miR) therapy with conventional chemotherapy in vitro and in vivo to determine whether co-delivery enhances anti-tumor efficacy compared to high-dose chemotherapy alone.

Methods: Bioengineered miR-124 and miR-34 fused to a human tRNA-glycine scaffold were used, and uptake was confirmed by RT-qPCR. Combined effects of miR therapy and cisplatin were evaluated in vitro using cell viability and TUNEL assays in Be(2)-C, SK-N-SH, and NB1643 HRNB cell lines. For in vivo studies, 2×10^6 cells were injected subcutaneously into NSG mice, followed by intratumoral miR treatment of either miR-124 or miR-34 combined with intravenous cisplatin (10 mg/kg) once tumors reached the target size. Tumor growth and miR upregulation were assessed through endpoint monitoring and RT-qPCR and compared to mice treated with low or high-dose cisplatin alone (10 or 20 mg/kg). Control groups received saline only.

Results: In vitro, HRNB cells co-treated with miRs and cisplatin showed a significant reduction in cell viability compared to cisplatin treatment only across all concentrations. In vivo, HRNB tumors treated with combination therapy showed a marked reduction in tumor size, surpassing the efficacy of both low dose cisplatin (10mg/kg) and high dose (20mg/kg) alone. Notably, half of SK-N-SH tumors demonstrated complete tumor regression after combination therapy with either miRs.

Conclusion: In both in vitro and in vivo HRNB models, the combination of miRs and cisplatin demonstrated significantly enhanced therapeutic efficacy and suggests the potential for dose-reduction of the required chemotherapy for clinical efficacy, which is particularly valuable in pediatric oncology. These promising results support the need for further investigation into miRNA-based combination therapies as a therapeutic strategy for children with HRNB.

Lay Language Abstract: High-risk neuroblastoma is an aggressive childhood cancer, and current treatments often require high doses of chemotherapy that can cause serious side effects. In this study, we tested a new strategy that combines chemotherapy with microRNAs, small molecules that help regulate how genes behave in cancer cells. In cell based and mouse models of neuroblastoma, this combination treatment reduced tumor growth more effectively than chemotherapy alone, even at higher doses. In some cases, tumors completely disappeared after treatment. These results suggest that microRNA-based therapies may help make cancer treatment more effective while potentially allowing for lower chemotherapy doses for children.

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3 BRD2 UPREGULATION AS A PAN-CANCER ADAPTIVE RESISTANCE MECHANISM TO BET INHIBITION

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Bromodomain and extraterminal motif (BET) inhibitors, such as JQ1, are promising cancer therapeutics that target epigenetic regulators, particularly BRD4. However, resistance to BET inhibitors (BETi) limits their clinical utility, necessitating a better understanding of adaptive mechanisms. We identified BRD2 upregulation as a conserved response to BET inhibition across multiple cancer types and hypothesized that BRD2 compensates for BRD4 loss, sustaining essential transcriptional programs upon treatment. Consistent with this, BRD2 knockdown sensitized cancer cells to BETi in vitro, and combining BRD2 depletion and JQ1 treatment significantly impaired tumor growth in vivo. At the chromatin level, BRD2 and BRD4 ChIP-seq analysis of pancreatic cancer cells showed consistent BRD4 loss from chromatin after JQ1 treatment, while BRD2 displacement differed by sensitivity. Resistant cells maintained higher BRD2 occupancy than sensitive cells, suggesting a link between BRD2 retention and drug response. Mechanistically, NFYA mediates BRD2 upregulation as NFYA depletion attenuated BRD2 upregulation upon BETi treatment. Collectively, our findings establish BRD2 as a critical mediator of pan-cancer adaptive resistance to BETi and identify NFYA as a novel transcriptional regulator of this process. Co-targeting BRD2 or its regulatory network offers a rational strategy to enhance the durability and efficacy of BET-based therapies.

Lay Language Abstract: BET inhibitors are cancer drugs designed to block proteins that control which genes are turned on, but many tumors eventually become resistant. In my research, I found that cancer cells often respond by increasing a related protein called BRD2, which can help them keep important gene programs running despite treatment. When we lower BRD2, BET inhibitors work much better in cells and tumors grow more slowly in mice. This suggests that combining BET inhibitors with strategies that block BRD2 could make these therapies more durable and effective.

4 A COMMUNITY-PARTNERED FRAMEWORK FOR INCREASING ACCESS TO CANCER GENOMIC MEDICINE RESEARCH TO IMPROVE CANCER HEALTH OUTCOMES FOR NATIVE AND INDIGENOUS COMMUNITIES

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In the US, Native and Indigenous communities (American Indians and Alaska Natives) experience some of the most substantial cancer health disparities, with the highest comorbidity rates and lowest 5-year survival rates for all major cancer types. Despite this high burden of disease, Native communities remain severely underrepresented in preclinical cancer research data and clinical trials that drive advancement of cancer prevention and treatment. This has been largely driving by a history of extractive research practices and lack of community engagement in research. Ultimately, underrepresentation has deprived Native communities from the benefits of cancer genomic medicine and exacerbated existing health disparities. In this study, we present a community-partnered framework for ethical and equitable engagement of Native communities in cancer genomic medicine research. Working with a community advisory board of Native health leaders, we developed

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the Native Cancer Health and Research Interest Assessment tool to 1) identify cancer health priorities for participating Native communities and 2) understand the expectations of Native community members for their research participation experience. We administered the assessment in partnership with Tribal health programs in Northern California. Our results (n=149) show that Native communities in Northern California see cancer as a significant health issue. While the majority of Native community participants said they were willing to donate a biospecimen for cancer research purposes, less than 10% reported having been asked to previously participate in research and only 15% of participants felt they had a moderate or high level of knowledge about the biospecimen donation process. When asked about factors that would most influence their decision to donate a biospecimen for research purposes, participants reported Native representation on the research team, compensation, and personal and community benefit as positive factors. Lack of transparency and lack of reconsent in secondary sample/data use negatively affected willingness to donate a biospecimen. Our study highlights the critical need to engage Native communities early and consistently throughout the research process to develop participation methods that work best for participating communities. Ultimately, this innovative “community co-design” framework will support greater Native community participation in cancer genomic medicine research for effective improvements to Native cancer health.

Lay Language Abstract: Native an Indigenous communities experience a high burden of cancer, with more diagnoses and deaths caused by cancer than other communities in the US. However, Native communities are not represented in the current research data that informs the development of new cancer prevention and treatment options, so these communities are not able to benefit from advancements. Through Tribal health partnerships in Northern California, we show that Native community members understand the value of participating in research but also expect that researchers engage Native communities to co-develop the research topics, research methods, and return of research benefits. This framework will ultimately promote ethical and equitable Native community participation in cancer research.

5 CHROMATIN ACCESSIBILITY DIFFERENTIATES CANCER ASSOCIATED FIBROBLAST SUBTYPES IN PANCREATIC CANCER

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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 to enhance PDAC treatment has not yet been successful due to the lack of understanding in CAF activation, heterogeneity, and plasticity. Previous scRNA-seq studies revealed different CAF subtypes with diverse phenotypes and functions but the underlying mechanisms of CAF activation remain unclear. 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 are characterized by their cellular states rather than an end-of-point differentiation. Therefore, we hypothesized 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 and inflammatory fibroblasts in vitro. Gained differentially accessible regions were identified across genomes, located not only at promoters but also at enhancers, and they were highly associated with transcriptional signatures of each subtype. In line with this, analysis on snATAC-seq of the fibroblast population within PDAC tumor tissues of both human patients and mouse models also confirmed the

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distinct chromatin accessibility profiles of different CAF subtypes. Interestingly, by overlaying with snRNA-seq, we discovered that chromatin structure of CAF was primed to be accessible towards late-stage myofibroblast subtype during tumorigenesis. Overall, our study demonstrates the epigenetic basis of CAF plasticity both in vitro and in vivo, suggesting a novel therapeutic strategy of epigenetically targeting CAF to remodel the stroma and improve treatment outcomes in PDAC patients.

Lay Language Abstract: Pancreatic ductal adenocarcinoma (PDAC) remains the deadliest cancer with only 13% of five-year survival rate in patients. Effective drug delivery to PDAC tumor has been limited due to the various functions of CAFs – a group of cells that majorly contribute to the fibrotic microenvironment of the tumor. Unfortunately, little is known about how different CAF subtypes arise and therefore targeting CAFs has not yet been successful for PDAC treatment. Interestingly, unlike cancer cells, CAFs do not carry genetic mutations. Instead, they simply switch between subtypes in response to external signals from cancer. We believe this "plasticity" is controlled by how genes are differently accessed – a process known as chromatin accessibility – to produce functional proteins. Using cell culture models to mimic CAF subtypes and advanced technology to look at the tumor at single-cell resolution, we found that different CAF subtypes have distinct patterns of chromatin accessibility. This will potentially offer a novel strategy to target CAFs and improve PDAC treatment.

6 A FUNCTIONAL–DIGITAL PRECISION ONCOLOGY PLATFORM INTEGRATING AI HISTOLOGY AND 3D BIOPRINTED TUMOROIDS TO PREDICT THERAPEUTIC RESPONSE

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Accurately predicting therapeutic response remains a major challenge in precision oncology. Existing preclinical models frequently fail to capture the structural organization, immune context, and functional dynamics of the human tumor microenvironment (TME). Conventional 2D culture systems oversimplify tumor–stromal interactions, while murine models lack autologous human immune components and often fail to recapitulate patient-specific treatment responses. To address these limitations, we developed a patient-derived 3D-bioprinted tumoroid platform that preserves tumor architecture and immune context within a collagen-based hydrogel matrix. Dissociated tumor specimens are bioprinted into structured tumoroids that maintain tumor, stromal, and immune components, enabling functional interrogation of therapeutic response through live readouts including viability, cytokine signaling, and immune activation. This platform has been successfully implemented across multiple malignancies, including bladder and prostate cancer, enabling high-throughput functional testing of patient-specific drug responses in a physiologically relevant tumor microenvironment.

To extend predictive capability and clinical translation, we integrated this functional system with Cellular Morphometric Biomarkers (CMBs), an artificial intelligence framework developed by collaborators that extracts quantitative morphometric signatures from routine hematoxylin and eosin (H&E) pathology slides. CMB models quantify spatial tumor–stromal architecture and have demonstrated the ability to predict therapeutic response directly from histologic morphology. We hypothesized that integrating digital histologic biomarkers with functional 3D tumor modeling would provide a cross-platform framework for therapy response prediction. To test this approach, we evaluated concordance between a previously developed 13-CMB model predicting androgen deprivation therapy (ADT) response and functional responses measured in patient-derived 3D

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tumoroids treated with darolutamide and enzalutamide. Across 10 matched patient samples, CMB-predicted resistance demonstrated strong agreement with tumoroid drug response, with a weighted Spearman correlation of ρ = 0.88 (p = 0.004) and a receiver operating characteristic AUC of approximately 0.93 for identifying ADT-resistant tumors. These findings demonstrate strong biological alignment between AI-derived morphologic predictors and live ex vivo tumor response phenotypes.

Together, these results establish an integrated functional–digital precision oncology platform that combines AI-derived histologic biomarkers with patient-specific 3D tumor modeling, enabling biologically grounded prediction of therapeutic response and providing a scalable strategy for functional precision medicine.

Lay Language Abstract: Our group has developed a 3D-bioprinted cell culture platform that enables us to perform high-throughput drug screens on patient tumors. Our inclusion of tumor, stromal, and immune components allows us to better replicate the tumor microenvironment, enabling physiologically relevant characteristics that can guide optimized chemotherapeutic regimens. To test clinical translational capabilities, we compared our 3D-bioprinted model with an existing AI-driven framework that predicts therapeutic response from imaging slides. The strong alignment between the AI-driven CMB signatures and our 3D-briprinted model provides a biologically grounded way to predict therapeutic response for patients.

7 EFFECTS OF A 28-DAY KETOGENIC DIETARY INTERVENTION ON INTRAHEPATIC FAT CONTENT AND BIOACTIVE LIPIDS: A PILOT RANDOMIZED CONTROLLED TRIAL

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Background & Aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a spectrum of progressive liver disease that affects 25% of the U.S. population and could progresses to cirrhosis and hepatocellular carcinoma (HCC). While weight loss with caloric restriction is recommended for MASLD treatment, it is unknown whether specific diets are more beneficial, as studies comparing diets with liver-specific endpoints are lacking. We hypothesize that a ketogenic diet (KD) will reduce more intrahepatic triglycerides and modulate bioactive lipid profiles compared to a standard weight loss diet (SD) among MASLD participants.

Methods: We conducted a pilot 2-arm randomized trial of a ketogenic vs. standard weight-loss dietary intervention to reduce MASLD progression. Participants were randomized according to sex. The primary aim was to evaluate the effect of the 4-week diet intervention on the change in intrahepatic triglyceride content measured by MRI proton density fat fraction (MRI-PDFF). Secondary endpoints included liver stiffness measured by magnetic resonance elastography (MRE), liver enzymes (AST and ALT), and patient-reported outcomes (constipation, fatigue, and cognitive function). For categorical variables, proportions were compared between groups using Fisher's exact test. Group differences in means or medians for quantitative variables were determined by t-test or Wilcox rank sum test. Plasma bioactive lipids and oxylipins were processed with MS-DIAL method and were analyzed using adjusted linear mixed-effects models to evaluate diet and time interaction.

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Results: 22 participants completed the intervention, SD (n=12) or KD (n=10) intervention: mean age, 56 vs 53 years; Male, 33% vs 50%; and Hispanic or Latino, 42% vs 30%. Compared to the SD, KD led to a more substantial decrease in PDFF (-46% ± 25% vs -25% ± 27%, p=0.07). After adjusting for skeletal muscle mass and trunk lean mass, KD decreased significantly in relative PDFF than SD (p=0.008 & 0.032). Lipidomic analyses identified significant diet and time interactions predominantly in glycerophospholipids (GP) and sphingolipids (SP).

Conclusions: In this pilot trial, KD resulted in a significant relative decrease in PDFF compared to SD after adjusting for lean body compositions. Modulation of bioactive lipid pathways suggests mechanistic links between carbohydrate restriction and hepatic lipid remodeling.

Lay Language Abstract: Fatty liver disease is now one of the most common liver conditions worldwide and can quietly progress to serious problems like cirrhosis or liver cancer. We studied whether a short-term ketogenic diet—a low-carbohydrate, high-fat eating pattern—could reduce liver fat more effectively than a standard weight-loss diet. Using advanced MRI scans, we found that the ketogenic diet led to a larger reduction in liver fat over just four weeks. We also observed changes in blood lipid molecules linked to inflammation and metabolism, suggesting that dietary patterns may influence liver health beyond simple weight loss.

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Poster Presentations

1 AMPHIREGULIN (AREG) DECREASE DISTANCE MIGRATED IN KRAS-Q61R AND BRAF-V600E CELLS

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RAS proteins (HRAS, NRAS, and KRAS) are key molecular switches that control cell growth and survival. Mutations—especially in KRAS—cause constant activation of signaling pathways, promoting uncontrolled proliferation and cancer development.

We studied mouse embryonic fibroblasts expressing wild-type or mutant RAS variants (HRAS_wt, NRAS_wt, KRAS_wt, KRAS_G12C, G12D, G12V, Q61R) and BRAF_V600E to assess how RAS activation influences cell behavior. Cells were cultured with or without the growth factor amphiregulin (AREG) and analyzed using ImageJ. Student groups investigated specific aspects of cell biology, including cell death, migration, shape, and division.

Across experiments, oncogenic RAS expression produced changes in cell phenotype, often intensified by growth factor treatment. These results show that active RAS signaling reprograms normal fibroblasts toward cancer-like behaviors, illustrating how genetic and environmental cues together shape cellular transformation.

2 INCREASED MIGRATION OF MICE CELLS WITH MUTATED KRAS PROTEIN EXPOSED TO GROWTH FACTOR

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RAS proteins (HRAS, NRAS, and KRAS) are key molecular switches that control cell growth and survival. Mutations—especially in KRAS—cause constant activation of signaling pathways, promoting uncontrolled proliferation and cancer development.

We studied mouse embryonic fibroblasts expressing wild-type or mutant RAS variants (HRAS_wt, NRAS_wt, KRAS_wt, KRAS_G12C, G12D, G12V, Q61R) and BRAF_V600E to assess how RAS activation influences cell behavior. Cells were cultured with or without the growth factor amphiregulin (AREG) and analyzed using ImageJ. Student groups investigated specific aspects of cell biology, including cell death, migration, shape, and division.

Across experiments, oncogenic RAS expression produced changes in cell phenotype, often intensified by growth factor treatment. These results show that active RAS signaling reprograms normal fibroblasts toward cancer-like behaviors, illustrating how genetic and environmental cues together shape cellular transformation.

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3 DIET-INDUCED CHANGES IN THE TUMOR MICROENVIRONMENT AND METABOLIC LANDSCAPE ACCELERATE HEAD AND NECK SQUAMOUS CELL CARCINOMA PROGRESSION 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) has been shown to promote cancer progression by inducing inflammation and immunosuppression. We developed an SCC murine cell line derived from a gain-of-function KrasG12D mutation and deletion of the Smad4 tumor suppressor in keratin (K15)-positive stem cells, closely mimicking the clinical progression of HNSCC tumors. The SCC cells were orthotopically implanted into the buccal mucosa of mice. The mice started their respective diets on the day of tumor implantation, receiving either regular chow or WD. Saliva samples were collected weekly. At endpoint, tumors, saliva, cecum content, and plasma were collected for analysis. Metabolomic profiling, 16S rRNA sequencing, spatial transcriptomics, and immunostaining were performed on samples to elucidate mechanisms contributing to SCC progression. Oral tumor-bearing mice on a WD exhibit more aggressive tumor progression, as indicated by increased tumor volume and histopathological analysis, compared to those on a regular diet. Tumors in the WD group display an increased presence of cancer stem cell signatures relative to controls. Spatial transcriptomics revealed reduced macrophages and fibroblasts in the stroma of WD tumors, indicating diet-induced changes in the TME. Additionally, saliva samples from WD tumor-bearing hosts reveal distinct metabolite profiles of both host and microbial origin. Our findings indicate that a WD promotes a tumor-supportive microenvironment in HNSCC by altering the TME and metabolomic landscape, underscoring diet as a modifiable factor in HNSCC progression and a potential therapeutic target. (Supported by Diversity Supplement under HNSCC SPORE.)

Lay Language Abstract: Head and neck squamous cell carcinoma (HNSCC) is an aggressive cancer strongly linked to tobacco, alcohol, and HPV, but environmental factors such as diet may also influence disease progression. In this study, we used a mouse model of oral cancer to compare the effects of a regular diet (RD) and a Western diet (WD) which is high in fat and sugar. Mice fed the WD developed larger, more aggressive tumors and showed an increase in tumor promoting cells along with a reduction in beneficial immune and support cells within the tumor microenvironment. Additionally, saliva and blood analyses revealed metabolic changes associated with the WD. These findings suggest that a Western diet can promote HNSCC progression by altering systemic metabolism and the tumor microenvironment.

4 METABOLOMIC AND LIPIDOMIC PROFILING REVEALS DISTINCT SUBTYPES OF IDH-WILDTYPE GLIOBLASTOMA AND SHARED METABOLIC FEATURES WITH IDH-MUTANT ASTROCYTOMA 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 = 9x10-5) and sorbitol (FC 3.9, p = 0.003), and decreases in ribonic acid (FC -3.3, p = 1.6x10-13) and arabitol (FC -2.9, p = 4.1x10-20). 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=7.5x10-4). 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=4.4x10-5) and decreases in phosphatidylcholine 39:7 (FC -2.8, p=3.0x10-19) , 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.

Lay Language Abstract: This study analyzed the chemical "fuel" sources of aggressive brain tumors to better understand how they grow. By comparing tumor tissue to healthy brains, we discovered that Glioblastoma isn't uniform; instead, it splits into three distinct metabolic subtypes, each relying on different metabolic pathways. Additionally, they confirmed that a different tumor type, IDH-mutant astrocytoma, is marked by a massive spike in a specific chemical called 2-hydroxyglutarate. These findings suggest that identifying a tumor's specific metabolic "personality" could help doctors create more personalized and effective treatment strategies in the future.

5 TOWARDS AUTOMATED PERSONALIZED DOSIMETRY FOR TARGETED RADIOPHARMACEUTICAL THERAPY

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In nuclear medicine, radiopharmaceuticals can be directly injected into patients to treat cancer and may be imaged using SPECT or PET. The specificity of a radiopharmaceutical for a molecular target makes it highly relevant for metastasized cancer, where distant tumour sites can be reached by binding to receptors expressed in malignant tissues. To quantify the deposited energy in tissues from ionizing radiation and its potential effects on the patient, personalized dosimetry is necessary. Monitoring the dose in radiopharmaceutical therapies can only be done retroactively, yet treatment can be optimized by identifying absorbed dose values between treatment cycles. Imaging must be done after each cycle to monitor the uptake, as this varies for each individual. However, personalized dosimetry workflow for radionuclide therapy is complex. Tumours and organs-at-risk segmentation, correct modelling, and activity-to-dose conversion necessitate various modalities and skills. We propose here a dosimetry pipeline integrating open source software resources for segmentation and dose estimation. The goal of our workflow is to leverage the possibility of personalized dosimetry to be automatic and integrated.

Our dataset comes from patients diagnosed with metastatic castrate-resistant prostate cancer (mCRPC) which were administered multiple cycles of Lu177-PSMA-617. Lu177-PSMA is a beta- emitter targeted at prostate membrane antigens, overexpressed by mCRPC cells. Our goal is to reach results comparable to the current standard of care for internal radiotherapy in the clinic, where the mean organ dose is obtained from semi-manual segmentation (MIM), fit of the imaging timepoints according to the exponential decay and activity to dose conversion according to the MIRD scheme. Standard dose conversion values per organ are used. The novelty of our research is the integration of the particle simulation tool GATE based on Geant 4 which estimates dose rates per voxel from activity maps with the goal of developing high precision bone marrow dosimetry. The absorbed dose derived per voxel accounts for tissue heterogeneity and provides potentially higher personalization capacity from individual dose conversion factors.

Lay Language Abstract: Radiopharmaceutical therapy uses radioactive drugs that can both target and treat cancer throughout the body but understanding how much radiation each organ receives is challenging. The current study of dosimetry requires multiple imaging and calculation steps, making it difficult to apply consistently for every patient. We are developing an automated pipeline that uses medical images and computer simulations to estimate radiation dose more accurately and with less manual work. By improving how dose is measured after each treatment cycle, this approach could help personalize therapy for patients with advanced prostate cancer and make treatments safer and more effective.

6 UNTARGETED METABOLOMIC PROFILING IN HUMAN GLIOMAS

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Introduction: Gliomas constitute the most prevalent primary malignancies of the central nervous system, with glioblastoma (GBM) representing the most lethal subtype, characterized by a median survival of approximately

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15 months despite maximal therapeutic intervention. Contemporary classification paradigms, while increasingly informed by molecular and genomic stratification, remain insufficient to capture the dynamic metabolic reprogramming that underpins gliomagenesis and therapeutic resistance. Metabolomics—the high-throughput interrogation of the small-molecule landscape within cells and tissues—has emerged as a powerful systems-level approach capable of elucidating the biochemical architecture of tumor biology. By resolving the metabolic signatures that govern tumor proliferation, immune evasion, and microenvironmental adaptation, metabolomic profiling offers an unprecedented window into actionable disease mechanisms. Here, we leverage untargeted metabolomic and lipidomic profiling to identify novel diagnostic biomarkers and exploit metabolic vulnerabilities in molecularly defined human gliomas.

Methods: We conducted comprehensive untargeted metabolomic and lipidomic profiling on 63 surgically resected human brain tissue specimens encompassing glioblastoma (n=38), IDH-mutant astrocytoma(n=4), and histologically noncancerous brain parenchyma (n=21). High-resolution mass spectrometry–based platforms were employed in collaboration with specialized metabolomics core facilities to quantify hundreds of endogenous metabolites spanning diverse biochemical classes. Differential abundance was assessed using volcano plot analyses and supervised multivariate modeling via partial least squares discriminant analysis (PLS-DA) to delineate metabolic divergence across diagnostic categories.

Results: Our analyses identified 2-hydroxyglutarate (2-HG) as a robust and highly discriminatory biomarker that unequivocally distinguishes IDH-mutant astrocytoma's from both glioblastoma and non-neoplastic brain tissue, reinforcing its oncometabolic significance. Strikingly, glioblastoma specimens exhibited a profoundly remodeled lipidome, characterized by marked enrichment of complex lipid species — indicative of voracious lipid consumption to sustain membrane biogenesis and fuel energy production. These lipidomic alterations are consistent with the elevated metabolic flux and proliferative capacity that define the aggressive GBM phenotype. Supervised multivariate modeling via PLS-DA achieved clear and reproducible separation of tumor subtypes, with lipid species emerging as principal drivers of inter-group variance. Collectively, these findings delineate both a clinically translatable diagnostic biomarker and a previously underappreciated lipid-centric metabolic phenotype unique to high-grade gliomas.

Conclusion: This study establishes that untargeted metabolomic profiling captures biologically critical dimensions of glioma pathophysiology that remain invisible to conventional histopathological and genomic approaches. The robust identification of 2-hydroxyglutarate (2-HG) as a discriminatory oncometabolite — the sine qua non of IDH-mutant astrocytoma — underscores its translational potential as a non-invasive biomarker for diagnostic stratification and longitudinal therapeutic monitoring. The discovery of a distinctly remodeled lipid landscape in glioblastoma exposes a metabolic dependency that may be therapeutically exploitable through targeted disruption of lipid biosynthetic and signaling pathways. Integration of metabolomic profiling into clinical decision-making frameworks stands to substantially advance precision oncology for patients with glioma. Ultimately, this work provides a compelling rationale for the metabolic targeting of glioblastoma and lays out the groundwork for the next generation of metabolism-directed therapeutic strategies.

Lay Language Abstract: Brain tumors like glioblastoma are very difficult to treat, partly because we don’t fully understand how they grow. Instead of only looking at genes, this study examines the small chemical molecules tumors produce, which act like fingerprints of their activity. We found that one molecule, called 2-hydroxyglutarate, can help identify certain types of tumors without invasive procedures. We also discovered that aggressive tumors rely heavily on fats to grow, which may be a weakness doctors can target. These findings could lead to better ways to diagnose brain tumors and develop more effective treatments.

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7 NONINVASIVE SPATIAL AND FUNCTIONAL TRACKING OF NANOENGINEERED NK CELLS USING ULTRASOUND-GUIDED PHOTOACOUSTIC IMAGING

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Introduction: Adoptive natural killer (NK) cell therapy holds significant potential as an off-the-shelf cancer immunotherapy, yet noninvasive, real-time assessment of infused NK cell localization and cytotoxic activity within the tumor microenvironment (TME) remains unexplored. To address this gap, we engineered a multiplexed nanoparticle (NP) system comprising two components: a gold nanosphere (GNS)-based photoacoustic (PA) nanosensor that responds to Granzyme B (GzmB), a key protease secreted by cytotoxic NK cells, and an indocyanine green (ICG)-loaded poly(lactic-co-glycolic acid) (PLGA) NP label for spatial NK cell tracking. Both NPs generate distinct PA signals detectable under multi-wavelength ultrasound/photoacoustic (US/PA) imaging.

Methods: The nanosensor was made by functionalizing GNSs with a GzmB-cleavable peptide coating designed to trigger NP aggregation and a corresponding PA signal shift upon GzmB exposure. Sensitivity and selectivity were confirmed by incubating the nanosensor with known GzmB concentrations and other catalytic enzymes. To assess functional performance, the nanosensor was co-incubated with soft tissue sarcoma cell lines and NK-92 cells, and PA signal changes were measured. In parallel, ICG-PLGA NPs were used to label NK-92 cells across multiple concentrations. The impact of labeling on NK cell viability, surface marker expression, migration, and cytotoxicity against multiple cancer cell lines was evaluated to confirm functional integrity. PA signal generation was then quantified by comparing labeled versus unlabeled NK cells in vitro.

Results: The GzmB nanosensor only aggregated in the presence of the enzyme GzmB, proving its selectivity. Co-incubation of the GNS nanosensor with NK-92-treated sarcoma cells produced a measurable PA signal shift, while no signal change occurred with untreated sarcoma cells or NK-92 cells alone, confirming nanosensor activation was specific to NK cell cytotoxic activity. ICG-PLGA labeling preserved NK cell viability and function across all assessed conditions, and labeled NK cells generated significantly higher PA signal than unlabeled controls in tissue-mimicking phantoms.

Conclusion: Together, these findings demonstrate that our two-component NP system can detect both the location and cytotoxic activity of NK cells in vitro. With further in vivo validation, this platform could serve as a powerful tool for real-time, noninvasive monitoring of adoptive NK cell therapy.

Lay Language Abstract: Cell-based cancer immunotherapy uses isolated immune cells from a patient or donor to target and kill cancer. One type of cell-based immunotherapy uses natural killer (NK) cells, which are very promising, but limited by a lack of ways to track the NK cells once inside the body. To overcome this, we designed two types of nanoparticles, one used to track the location of NK cells, and the other to show if they are active without requiring invasive procedures. We validated this system in cells outside a living organism, demonstrating they could be used to optimize and monitor cell-based cancer immunotherapy.

8 IDENTIFYING THE ROLE OF DDIT3 IN HIGH-GRADE SARCOMAS

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High-grade complex karyotype sarcomas are heterogeneous group of tumors and associated with poor outcomes primarily due to their tendency to develop metastatic disease. DDIT3, also known as C/EBP Homologous Protein (CHOP) is a dominant negative inhibitor of other C/EBP family members and is triggered by various stress stimuli such as DNA damage, ER stress, hypoxia, and amino acid starvation. Our lab performed a screen, informed by TCGA data to identify oncogenic drivers of sarcoma. DDIT3 was identified as one of the potential drivers of sarcoma development in the primary pooled genetic screening approach. However, in a secondary screen in which three genes of interest YAP1, KRAS, and DDIT3 were injected independently, only DDIT3 did not form tumors after 26 weeks. We examined the role of DDIT3 in high-grade sarcomas by co-expressing it with YAP1, a known oncogenic driver of sarcomas. Interestingly, it resulted in aggressive tumor development in vivo – short tumor latency, and a highly metastatic phenotype were observed. In addition, YAP1 DDIT3 could form sarcomas in the presence of tumor suppressors RB1 and TP53 which was not observed with other oncogenes that require loss of RB1 and TP53. With these findings, we conclude that DDIT3 is a facilitator of high-grade complex karyotype sarcomas, creating a permissive intracellular environment for transformation. Targeting of DDIT3 may elicit new therapeutic opportunities in sarcomas when its mechanism of action is understood and identified.

Lay Language Abstract: High-grade complex karyotype sarcomas are group of tumors that lead to poor outcomes. Our lab performed a screen to identify oncogenic drivers of sarcomas. With our data, we conclude that DDIT3 is a facilitator of high-grade complex karyotype sarcomas. Targeting of DDIT3 may may elicit new therapeutic opportunities.

9 FINANCIAL HARDSHIPS AND CHRONIC MEDICAL CONDITIONS IN ADOLESCENT AND YOUNG ADULT CANCER SURVIVORS

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Adolescents and young adult (AYA) cancer survivors face a higher risk of chronic medical conditions and are more likely to delay or forgo health care due to costs compared to same-age individuals without cancer. Gaps remain in our understanding of the financial hardships associated with cancer, its treatment, or the lasting health effects of treatment in AYA cancer survivors.

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In the Valuing Opinions and Insights from Cancer Experiences (VOICE) Study, participants diagnosed during 2016-2022 with 10 common AYA cancers between ages 15-39 years in California completed a survey in 2023-2024. Financial hardships were measured by financial debt (went into debt due to cancer) and 9 medical expense impact questions in the past year grouped into three domains (trouble meeting needs, asset depletion, and major financial changes). In addition, we assessed whether AYAs were diagnosed by a health care provider after cancer diagnosis with 10 chronic medical conditions. We examined the association of each financial hardship with 1 or ≥2 (vs 0) medical conditions using multinomial logistic regression, adjusting for covariates.

Among 3,562 AYAs, most were 30-39 years (71.3%), non-Hispanic (NH) White (35.7%) or Hispanic (33.5%), and had employer-sponsored insurance (66.8%). Nearly one-fifth (19.5%) of AYAs experienced financial debt since their diagnosis. In the past year, approximately one-third of AYAs experienced trouble meeting needs (28.5%) and asset depletion (32.8%), while 6.3% experienced major financial changes. In multivariable models, AYAs with ≥2 conditions were more likely to have financial debt (odds ratio (OR)=1.73, 95% confidence interval (CI) 1.45-2.06 vs. No medical conditions). AYAs with 1 (OR=1.20, CI 1.06-1.35) and ≥2 (OR=1.98, CI 1.68-2.32) medical conditions were more likely to have trouble meeting needs. AYAs with ≥2 conditions were also more likely to have asset depletion (OR=1.68, CI 1.43-1.97) and major financial changes (OR=2.05, CI 1.59-2.63).

Financial hardship impacts one-third of AYA cancer survivors, and AYAs with chronic medical conditions have a substantially greater likelihood of experiencing financial hardships. Our findings highlight the long-term financial impact of cancer in this population and the need to evaluate the effectiveness of targeted interventions, such as financial navigation, to address financial burden.

Lay Language Abstact: Adolescents and young adult (AYA) cancer survivors are likely to have long-term health issues due to cancer, its treatment, or other things going on in an AYAs life. These health issues may get harder to deal with if people cannot afford to get care for these health issues. We looked at survey questions to better understand some of the cost issues people may have and if there is any connection to getting health issues after being diagnosed with cancer. In our study, looking at cost issues from AYAs responding to the survey from 2023 to 2024, the more health issues that were reported, the greater the odds of having cost issues especially for AYAs that had two or more health issues.

10 BIOPRINTED 3D TUMOR MODEL CAN BETTER MODEL ANDROGEN SIGNALING DYNAMICS AND DRUG SENSITIVITIES IN TRAMP-DERIVED CELL LINE

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Transgenic adenocarcinoma of the mouse prostate (TRAMP) models are widely used to study prostate cancer biology and therapeutic response. Tumors arising in these mice can be harvested to generate TRAMP-derived cell lines that serve as experimental platforms for mechanistic and therapeutic investigations. However, conventional two-dimensional (2D) culture systems fail to recapitulate key features of the tumor microenvironment that influence androgen signaling and drug response. To address this limitation, we evaluated the behavior of TRAMP-derived prostate tumor cells in a three-dimensional (3D) bioprinted tumor model designed to better preserve tumor architecture and signaling context.

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Two aggressive TRAMP tumors were used to generate cell lines that were expanded and incorporated into a collagen-based 3D bioprinted system. Immunofluorescence analysis confirmed retention of key prostate cancer markers, including prostate-specific membrane antigen (PSMA) and NKX3.1. Functional studies revealed a strong androgen-dependent phenotype. In particular, the TRAMP–derived 255 cell line failed to establish or maintain growth in 3D culture without dihydrotestosterone (DHT), indicating persistent androgen dependence. Importantly, this androgen-supported growth was selectively inhibited by the androgen receptor antagonist darolutamide in the 3D system. Notably, this darolutamide sensitivity was not observed in conventional 2D culture, highlighting a context-dependent therapeutic response revealed only in the 3D model. Together, these findings demonstrate that 3D bioprinted tumor models can uncover biologically relevant androgen signaling dynamics and drug sensitivities that are not evident in standard 2D systems. These models may therefore provide a more physiologically relevant platform for studying prostate cancer biology and evaluating therapeutic response.

Transgenic adenocarcinoma of the mouse prostate (TRAMP) models and TRAMP-derived cell lines are important tools in the study of prostate cancer therapeutics. However, traditional 2D models often fail to model components of the tumor microenvironment that are necessary to adequately the androgen signaling and drug mechanisms. To overcome this limitation, we are investigating the use of a 3D bioprinted system using two Lay

Lay Language Abstract: TRAMP-derived cell lines that show expression of key prostate-specific markers. These studies have shown that in 3D culture, these cell lines need the presence of androgens for survival while also showing sensitivity to androgen receptor targeting drugs, a characteristic that is not observed in 2D cultures. These findings indicate 3D models can provide a more physiologically relevant platform for the study of prostate cancer biology.

11 BRAF-V600E CELLS SHOW GREATER APOPTOTIC SENSITIVITY WITHOUT GROWTH FACTORS THAN WITH AREG

Angela Le and Joji Tomii, High School Students, Sheldon High School Biotechnology Academy, Elk Grove, CA

RAS proteins (HRAS, NRAS, and KRAS) are key molecular switches that control cell growth and survival. Mutations—especially in KRAS—cause constant activation of signaling pathways, promoting uncontrolled proliferation and cancer development.

We studied mouse embryonic fibroblasts expressing wild-type or mutant RAS variants (HRAS_wt, NRAS_wt, KRAS_wt, KRAS_G12C, G12D, G12V, Q61R) and BRAF_V600E to assess how RAS activation influences cell behavior. Cells were cultured with or without the growth factor amphiregulin (AREG) and analyzed using ImageJ. Student groups investigated specific aspects of cell biology, including cell death, migration, shape, and division.

Across experiments, oncogenic RAS expression produced changes in cell phenotype, often intensified by growth factor treatment. These results show that active RAS signaling reprograms normal fibroblasts toward cancer-like behaviors, illustrating how genetic and environmental cues together shape cellular transformation.

12 COMPARING CELL DIVISION IN MOUSE EPITHELIAL KRAS-AREG CELLS

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Ava Allen, Tram Nguyen, and Malia Ann Gomez, High School Students, Sheldon High School Biotechnology Academy, Elk Grove, CA

RAS proteins (HRAS, NRAS, and KRAS) are key molecular switches that control cell growth and survival. Mutations—especially in KRAS—cause constant activation of signaling pathways, promoting uncontrolled proliferation and cancer development.

We studied mouse embryonic fibroblasts expressing wild-type or mutant RAS variants (HRAS_wt, NRAS_wt, KRAS_wt, KRAS_G12C, G12D, G12V, Q61R) and BRAF_V600E to assess how RAS activation influences cell behavior. Cells were cultured with or without the growth factor amphiregulin (AREG) and analyzed using ImageJ. Student groups investigated specific aspects of cell biology, including cell death, migration, shape, and division.

Across experiments, oncogenic RAS expression produced changes in cell phenotype, often intensified by growth factor treatment. These results show that active RAS signaling reprograms normal fibroblasts toward cancer-like behaviors, illustrating how genetic and environmental cues together shape cellular transformation.

13 DEVELOPING POLYGENIC RISK SCORES TO IMPROVE PREDICTION OF HER2+ BREAST CANCER IN HISPANIC/LATINA WOMEN

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Breast cancer is the most frequently diagnosed cancer in the United States (US) and the second leading cause of cancer death among US women. Hispanic/Latina (H/L) women are more likely to develop more aggressive breast cancer tumor subtypes, such as human epidermal growth factor 2 receptor (HER2)-positive or Hormone Receptor (HR)-negative disease, than non-Hispanic white women. Polygenic risk scores (PRS) have been developed to predict an individual's genetic predisposition for developing breast cancer. Most available PRS are focused on the prediction of overall breast cancer risk and are most predictive for HR+ and HER2- tumors and less effective for other subtypes. Most PRS panels have been developed based on genetic variants found in European ancestry, leading to underperformance in women of different ancestries. To develop PRS panels for H/L women that predict intrinsic subtypes with HER2+ status (both HR+/-), we utilized overall breast cancer PRS panels that have been based on European ancestry and added two subtype-specific H/L variants and a new variant discovered in a H/L women HER2+ GWAS. PRS performance was evaluated using multivariable logistic regression and the area under the Receiver Operating Characteristic (ROC) curve. This resulted in a PRS panel with 234 genetic variants that is predictive for both HR+/HER2+ (OR = 1.74, AUC = 0.649) and for HR-/HER2+ (OR = 1.55, AUC = 0.623) breast cancer in Peruvian women, which outperformed the overall breast cancer PRS panel developed in European ancestry studies. Future directions include developing PRS panels that predict other breast cancer subtypes and utilize other PRS development methods to improve prediction of breast cancer subtype-specific PRS panels.

Lay Language Abstact: Breast cancer is one of the leading causes of cancer deaths in women in the United States, especially in Hispanic/Latina women who develop more aggressive tumor subtypes more often. There are genetic prediction models made to identify women who are at a high risk of developing overall breast cancer, but there are none for breast cancer subtypes in Hispanic/Latina women. We developed a prediction

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model that predicts aggressive breast cancer tumor subtypes in Hispanic/Latina women. Better prediction will help treat women by improving screening strategies and personalizing prevention and treatment options.

14 THE CALIFORNIA FIREFIGHTER CANCER RESEARCH STUDY (CAFF-CRS): COHORT PROFILE AND BASELINE ASSESSMENT OF METABOLIC AND OCCUPATIONAL RISK FACTORS

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Introduction. Cancer is the leading cause of death among California firefighters (CA-FFs). Occupational firefighting exposes CA-FF to numerous chemical, physical, mental, and behavioral hazards that contribute significant risks for cancer. Examination of occupation-related cancer risks in California firefighters will serve to elucidate preventive interventions.

Methods. Participants recruited between 2024-2025 completed baseline blood donation, body composition testing, vitals and clinical lab testing, nutritional assessment, and numerous validated questionnaires. Participants were also asked to continuously wear a study-issued Fitbit to measure sleep, heart rate, and activity levels for 12 months.

Results. A cohort of 712 firefighters were enrolled (mean age, 39 years; female, 5%; Hispanic or Latino, 23%; mean years of service, 12 years). Cancer was a top health concern for 86% of participants, yet only 16% were aware of USPSTF cancer screening guidelines. Poor sleep quality and fatigue were prevalent; 78% of participants had worse sleep and 76% had worse fatigue compared to the national average. Objectively assessed sleep indicates an inverse association between sleep time and sleep efficiency with the number of incidents responded to in a typical shift. Most ever tobacco users report quitting, with only 1% reporting current cigarette smoking and 8% reporting current smokeless tobacco use. On the other hand, use of nicotine pouches was highly prevalent (30%). A higher heart rate, lower heart rate variability, and higher blood pressure were observed among nicotine users compared to non-users. Dietary assessment revealed high saturated fat and low grain consumption in CA-FF, associated with elevated cholesterol levels. Alcohol use varied across rank and age; younger CA-FF were more likely to binge drink. Adverse mental health was associated with an increase in binge drinking habits. Lastly, there was a high prevalence of hypertension in CA-FF compared to age-matched California adults.

Conclusions. CA-FF face diverse cancer risks due to occupation-related health effects. Future analyses will examine biomarkers of exposure to illustrate the biological mechanisms of cancer risk and develop evidence-based strategies to reduce cancer in firefighters.

Lay Language Abstreact: Firefighters in California face an elevated risk of cancer due to occupational health effects. In this cohort study, comprehensive clinical testing, wearable monitoring, and validated questionnaires revealed prevalent risks including poor sleep linked to shift incident load, nicotine use associated with adverse cardiovascular markers, unhealthy dietary patterns, alcohol consumption habits linked to adverse mental health events, and high prevalence of hypertension. Examining occupation-related cancer risks in California firefighters is critical for developing targeted evidence-based preventive interventions.

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15 OBESITY EXACERBATES CYTOKINE RELEASE SYNDROME (CRS)-LIKE TOXICITY ASSOCIATED WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY IN PRECLINICAL MODELS

Wahed Firoz, Graduate Student[1,2], Craig P. Collins[1], Logan V. Vick[2], Michael K. Sheng[1], Ryan N. Nielsen[1], Spencer Rosario[3], Robert J. Canter[3,4,6], Arta M. Monjazeb[2,6], Sean J. Judge[5,6], Shuchi Gulati[5,6], Anthony E. Zamora[5,6], William J. Murphy[1,5,6]
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Obesity is characterized by a state of meta-inflammation, excess adiposity, and metabolic perturbations. Although considered a negative co-morbidity for cancer and immune function, our lab has previously shown obesity exerts a beneficial role during immunotherapy, termed the “obesity paradox”. Chimeric antigen receptor (CAR) T cells have become a transformative immune cellular therapy for hematological malignancies and are increasingly applied towards solid tumors and autoimmunity. Given the pleiotropy of obesity and the widespread usage of CAR therapy, we aimed to assess the role of obesity in CAR T cell function and toxicity using a novel diet-induced obese (DIO) xenograft model. Immunodeficient NOD-scid IL2Rgnull (NSG) mice were fed a 10% low-fat diet or 60% high-fat diet for four months to generate lean and DIO cohorts, respectively. We observed significant but variable weight gain among the DIO mice along with metabolic perturbations regardless of adiposity by metabolomic assessment. Interestingly, Raji lymphoma growth was markedly increased in all DIO recipients. We then performed sub-lethal TBI (135cGy, X-ray) conditioning on day 8, and infused tri-specific CD19/CD20/CD22-targeting CAR T cells on day 9 post-tumor injection. Tissues and serum were collected at multiple time-points for flow cytometry immunophenotyping, histopathology, cytokine analysis, and metabolomics along with IVIS imaging for assessment of anti-tumor efficacy. We observed comparable anti-tumor effects across both DIO and lean groups after CAR T infusion. However, this also coincided with increased weight loss, mortality, and serum human and mouse pro-inflammatory cytokines (human IL-6, IFNg, TNF; mouse IL-1b, TNF) in the DIO cohort, suggestive of CRS. Overall, we observed negative prognostic effects of obesity on preclinical models of CAR T cells affecting both efficacy and off-target effects. Given the wide application of CAR therapy and high prevalence of obesity, further study of mechanisms driving worse outcomes after treatment and connection to clinical data is warranted.

Lay Language Abstract: Obesity is generally considered a negative factor in terms of cancer development and immune responses. However, our laboratory has shown obesity to have a paradoxically beneficial role in some immunotherapies. As a result, we aimed to assess if obesity has a similarly beneficial role for treating cancer using chimeric antigen receptor (CAR) T cells, which are a successful form of immune cell therapy. We found obesity to result in increased toxicity, yet did not worsen anti-tumor effects. Though further experiments are needed to establish a relationship between obesity with the anti-tumor efficacy and toxicity of CAR T cells.

16 SPATIAL TRANSCRIPTOMICS REVEALS NEIGHBORHOOD-DEPENDENT T CELL GENE EXPRESSION IN ORAL SQUAMOUS CELL CARCINOMAS

Jack B. Goon, Graduate Student[1,6], Siao-Yi Wang[1,2,6], Emanual Maverakis[1,3,6], Andrew C. Birkeland[4,6], Xiao-Jing Wang[1,56]

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One hallmark of cancer development is the impairment of the immune system. As such, immunotherapies are FDA-approved to treat many solid tumors. However, immunotherapy efficacy is limited to a subset of patients, in part due to the immunosuppressive tumor microenvironment (TME). The TME consists of several types of cells, each of which can be further divided into sub-populations that exist in spatial context. Thus, traditional techniques like flow cytometry and immunohistochemistry fail to fully represent the TME. To better understand how the TME contributes to cancer development and identify novel therapeutic targets, we utilized in-situ high-plex mRNA spatial profiling technology (10XGenomics Xenium platform) to profile human oral squamous cell carcinoma tumor sections (n=3 patients). Using machine learning to segment cells, multi-omics factor analysis (MOFA) to reconcile morphology data with mRNA transcriptional data, and unsupervised clustering to separate cell populations, we identified over 10 cell types in spatial context. Proximity analysis revealed that T cells and NK cells, along with other lymphocytes and stromal cells, often formed spatial niches separate from cancer cells. T cells were grouped into spatial neighborhoods based on their proximity to other lymphocytes, myeloid cells, and tumor cells. T cells in the tumor neighborhood differentially expressed effector-related genes such as GZMB, suggesting an active anti-tumor immune response once T cells can infiltrate the tumor. Furthermore, cancer cells were sub-clustered, revealing tumor heterogeneity within a given patient, as well as between patients. While limited in sample size, these findings provide deep insights into gene expression within the TME, for example revealing distinct T cell populations based on spatial context. Future analysis will reveal similar insights into myeloid populations. Ultimately, these findings will inform the development of drugs that target the TME to improve immunotherapy response in solid tumors.

Lay Language Abstract: Cancer is comprised of more than just cancer cells. T cells, the same white blood cells that help you fight off an infection like the flu, are trying to kill cancer cells. Other cells, so-called immunosuppressive cells, act to suppress T cell killing. My research uses the latest techniques to profile these cells in the spatial context of the tumor environment. Ultimately, these findings will inform drug development, particularly how we can target immunosuppressive cells to target T cell killing of cancer cells.

17 GENERATION OF CHIMERIC ANTIGEN RECEPTOR BEARING TUMOR INFILTRATING LYMPHOCYTES FOR TREATMENT OF HEAD AND NECK CANCER

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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. Current treatments include chemotherapy and immune checkpoint inhibitors. However, the majority of patients fail to respond to these treatments. In addition, patients often develop resistance to standard of care interventions, highlighting the need for more effective treatment strategies. Adoptive cellular therapy (ACT) has emerged as an exciting method to treat malignant disease. Recently, tumor infiltrating lymphocytes (TIL) therapy was approved for treatment of metastatic melanoma, marking the

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first FDA approved ACT for solid malignancies. To produce TIL, cancer-reactive T cells are isolated from patient tumors, stimulated to expand, and then re-infused into the patient. Though TIL therapy showed promising results in melanoma, it achieved only an 11% response rate in a trial for HNSCC. We hypothesize that addition of a chimeric antigen receptor (CAR), an engineered receptor that directly activates a T cell upon binding of its target, can augment the activity of TIL against HNSCC tumors and improve their therapeutic efficacy. In order to generate TIL cultures from a HNSCC patient, we digested and processed an oral squamous cell carcinoma (OSCC) tumor sample. We then selectively expanded T cells from the sample through CD3 stimulation and administration of IL-2. We subsequently characterized their phenotype by flow cytometry, revealing a population that was overwhelmingly CD3 positive. The culture had a skew towards a T stem central memory phenotype, a subset of CD62L+CD45RA+ CD28+ CD95+ cells distinguished by their capacity for self-renewal and resistance to exhaustion programs. In addition, we were able to quantify expression of exhaustion markers within the TIL population, a key metric for comparison in future studies. Following TIL isolation, cells were transduced with lentivirus encoding a CAR that targets B7-H3, a protein prevalent in HNSCC tumors. While only a subset of TIL were transduced, these findings indicate the feasibility of CAR TIL product generation. Ongoing studies aim to further elucidate phenotypic profiles, optimize TIL transduction, and evaluate the functionality of CAR TIL in vitro and in vivo.

Lay Language Abstract: Head and neck squamous cell carcinoma (HNSCC) patients have a poor prognosis after metastasis. A recent advance in adoptive cellular therapies is tumor infiltrating lymphocytes (TIL), in which cancer-reactive T cells are isolated from patient tumors, stimulated to expand, and then re-infused into the patient. TIL therapy has shown promise in treating metastatic melanoma but has a low response rate in HNSCC. We hypothesize that adding a chimeric antigen receptor (CAR), an engineered receptor that can directly activate a T cell, can augment the activity of TIL against HNSCC tumors and improve their therapeutic efficacy.

18 A VISION GUIDED HIGH-THROUGHPUT RAMAN MICROSCOPE ENABLING BLOOD LIQUID BIOPSY

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With tissue biopsy as the gold standard for cancer diagnosis, liquid biopsies that detect circulating tumor biomarkers in body fluids, such as circulating tumor DNA (ctDNA), proteins, and extracellular vesicles, offer a promising non-invasive option for large-scale screening; however, existing sequencing-based methods are costly, slow, and require engineered molecular labeling. Raman spectroscopy-based liquid biopsy provides rapid, label-free molecular analysis of biofluids through inelastic light scattering. Moreover, Raman spectroscopy captures a comprehensive molecular profile of patient metabolomic activity in a single measurement, rather than focusing solely on one specific type of biomarker, enabling sensitive detection of subtle biomolecular changes linked to cancer development in the earliest stages.

Despite its promise, accurate biochemical interpretation requires extensive preprocessing and expert analysis, which hinders clinical adoption. Furthermore, confounding patient covariates such as smoking and drinking status, and medical history, alter patients' metabolite profiles, thereby introducing additional variability into the resulting Raman spectra. Machine learning (ML) has been increasingly utilized to recognize cancer-related

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diagnostic fingerprint patterns in Raman spectra. However, current ML models are frequently trained on limited datasets of inconsistent quality, elevating the risk of overfitting and leading to poor predictive performance when applied to new patient samples, thereby restricting the generalizability and clinical utility of these methods.

In this study, we developed an automated, high-throughput Raman microscope guided by computer vision to collect a high-quality dataset from large patient cohorts and leverage scaling laws to train a robust cancer screening model using blood plasma. Starting with head and neck cancer patient cohorts, we demonstrated how this vision-guided microscope can help identify the most informative regions of the sample, scale up the data size, and improve our ability to classify cancer patients and healthy controls.

Lay Language Abstract: Cancer is most treatable when caught early, but current diagnostic methods often require invasive tissue biopsies or expensive genetic tests. This research develops a faster and less invasive platform for blood-based cancer screening that could make routine early detection accessible to far more people.

19 PHYSIOCHEMICAL INTERACTION DEPENDENT TRANSPORTATION OF POLLUTANT ADSORBED NANOPLASTIC (PANS) IN HUMAN LUNG ADENOCARCINOMA CELLS

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Microplastics are established vectors for pollutants, absorbing carcinogenic substances including polyaromatic hydrocarbons (PAHs), pesticides, and heavy metals pollution in the form of particulate matter. Particulate matter smaller than 2.5 μm (PM2.5) is classified as a group 1 carcinogen and can reach the alveoli in the lungs following inhalation. A recent Nature study highlighted the potential of PM2.5 to promote lung cancer in never smokers (LCINS). Compared to microplastics, smaller nanoplastics (<1 μm) can travel over long distances in the atmosphere and possess altered health risks via lung inhalation. Moreover, their increased surface area-to-volume ratio enhances their ability to adsorb pollutants, forming a complex material we term pollutant-adsorbed nanoplastics, or PANs. Nanoplastics have been linked to cancer progression by inducing pro-inflammatory responses, endocrine disruption, and oxidative stress, yet the alteration of these cellular functions because of nanoplastic interplay with small molecule pollutants found in complex atmospheric particulate matter (i.e., formation of PANs) is poorly understood. Current research on PAN toxicity provides limited characterization of their formation kinetics and affinity. The physiochemical interactions between pollutants and plastics drive PAN formation and their transportation and toxicity in the body. This research applies enhanced darkfield hyperspectral imaging (EDF-HSI) as a novel, label-free approach for single-particle chemical and spatial mapping of PANs, revealing how PANs exacerbate pollutant toxicity and carcinogenicity by resolving their composition and desorption in cells. EDF-HSI was used to chemically detect and spatially map spectral shifts in polystyrene diazinon (PSDZN) PANs compared to controls. Principle component analysis (PCA) revealed clustering of PSDZN compared to pristine PS. We evaluated changes in cell uptake of PSDZN PANs compared to PS and PS incubated in methanol solvent (PSMeOH) in human lung adenocarcinoma (A549) cells. Mean particle spectra were stratified by exposure condition and in/outside of cells for each exposure condition. PCA analysis revealed similar clustering of all groups, within and outside of cells except for PSDZN, which exhibited spectral shifts. This data established the feasibility of EDF-HSI for non-destructive, label-free, single-particle spatial and chemical characterization of PAN formation kinetics and interactions in cells and highlights the significance of pollutant adsorption on nanoplastic transportation in cells.

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Lay Language Abstract: Nanoplastics are extremely small particles that result from the degradation of plastic waste in the environment. Nanoplastics can interact with other carcinogenic chemicals and pollutants in the environment and facility their transport into the human body. We are using new microscopy techniques to understand how nanoplastics interact with the human body and how the adsorption of pollutants by nanoplastics alter their toxicity in the human lung.

20 EFFECTS OF DIHYDROARTEMISININ AND QUERCETIN ON PANCREATIC CANCER CELL VIABILITY

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Pancreatic ductal adenocarcinoma is one of the most aggressive malignancies and currently has an overall five-year survival rate of approximately 13% in the United States. The poor prognosis is largely attributed to late diagnosis, rapid disease progression, and resistance to existing therapies. These challenges highlight the need to investigate new therapeutic strategies. Bioactive compounds derived from natural sources have gained increasing attention due to their ability to influence oxidative stress, apoptosis, and cellular signaling pathways associated with tumor growth. This study evaluated the cytotoxic effects of dihydroartemisinin (DHA), an active metabolite of artemisinin, and the plant-derived flavonoid quercetin on pancreatic cancer cell growth. Human Panc-1 pancreatic cancer cells were cultured in 96-well plates and treated with DHA at increasing concentrations ranging from 5–40 μM (5, 10, 20, and 40 μM) for 48 and 72 hours to assess time-dependent cytotoxic effects. DHA treatment led to a concentration - dependent decrease in Panc-1 cell growth, with greater reductions observed at higher concentrations. In a separate experiment, pancreatic cancer cells were treated with Quercetin at concentrations of 5–40 μM and analyzed under similar conditions.This treatment also decreased pancreatic cancer cell growth.This study evaluates the cytotoxic effects of two bioactive compounds: dihydroartemisinin (DHA), a sesquiterpene lactone endoperoxide derived from artemisinin that induces oxidative stress through iron-dependent reactive oxygen species generation, and quercetin, a plant derived flavonoid known to influence cellular signaling pathways and modulate oxidative stress. Since these compounds influence cellular stress pathways through different distinct mechanisms, current studies suggest that both compounds may act through complementary pathways and exploration of their combined effects are of interest as potential synergistic strategies for targeting pancreatic cancer cells. Ongoing research is investigating the combined antitumor effects of DHA and Quercetin to determine whether these complementary bioactive compounds produce potentially synergistic cytotoxic effects against pancreatic cancer cells.

Lay Language Abstract: Pancreatic cancer is one of the deadliest cancers and has very limited treatment options. This research examines whether naturally derived compounds can reduce the survival of pancreatic cancer cells grown in the laboratory. Two compounds, dihydroartemisinin and quercetin, were tested to see how they affect cancer cell viability. Early results show that these compounds can reduce the metabolic activity of pancreatic cancer cells, suggesting potential anticancer effects. Understanding how these compounds work may help guide future studies exploring new strategies for targeting pancreatic cancer.

21 THE EFFECTS OF GROWTH FACTOR ON CELL DIVISION RATES IN KRAS CELLS

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RAS proteins (HRAS, NRAS, and KRAS) are key molecular switches that control cell growth and survival. Mutations—especially in KRAS—cause constant activation of signaling pathways, promoting uncontrolled proliferation and cancer development.

We studied mouse embryonic fibroblasts expressing wild-type or mutant RAS variants (HRAS_wt, NRAS_wt, KRAS_wt, KRAS_G12C, G12D, G12V, Q61R) and BRAF_V600E to assess how RAS activation influences cell behavior. Cells were cultured with or without the growth factor amphiregulin (AREG) and analyzed using ImageJ. Student groups investigated specific aspects of cell biology, including cell death, migration, shape, and division.

Across experiments, oncogenic RAS expression produced changes in cell phenotype, often intensified by growth factor treatment. These results show that active RAS signaling reprograms normal fibroblasts toward cancer-like behaviors, illustrating how genetic and environmental cues together shape cellular transformation.

22 CELL SPEED VARIABILITY OF KRAS MUTATIONS DETERMINED BY PRESENCE OF AREG IN CANCEROUS MICE CELLS

Maily Vue and Casydi Sin, High School Students, Sheldon High School Biotechnology Academy, Elk Grove, CA

RAS proteins (HRAS, NRAS, and KRAS) are key molecular switches that control cell growth and survival. Mutations—especially in KRAS—cause constant activation of signaling pathways, promoting uncontrolled proliferation and cancer development.

We studied mouse embryonic fibroblasts expressing wild-type or mutant RAS variants (HRAS_wt, NRAS_wt, KRAS_wt, KRAS_G12C, G12D, G12V, Q61R) and BRAF_V600E to assess how RAS activation influences cell behavior. Cells were cultured with or without the growth factor amphiregulin (AREG) and analyzed using ImageJ. Student groups investigated specific aspects of cell biology, including cell death, migration, shape, and division.

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23 ENVIRONMENTAL EXPOSURES AND DNA METHYLATION PATTERNS ASSOCIATED WITH BREAST CANCER RISK ACROSS GENERATIONS

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Environmental exposures during pregnancy have been linked to breast cancer risk and metabolic outcomes in subsequent generations, yet the underlying epigenetic mechanisms remain unclear. This study investigates DNA methylation (DNAm) patterns associated with perinatal DDT exposures and breast cancer risk indicators

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in the Child Health and Development Studies (CHDS), a three-generation cohort. Using DNAm data from 87 daughter–granddaughter pairs, we analyze genome-wide methylation profiles with the Comethyl bioinformatics pipeline to identify co-methylated genomic regions exhibiting correlated methylation changes. These regions are examined for associations with obesity and age at menarche, and known breast cancer in the daughter–granddaughter pairs. We further evaluate whether informative DNAm patterns overlap between generations and whether they are associated with grandparents' measured chemical exposures, including DDT. We hypothesize there will be alterations in breast cancer related genes such as BRCA1 and BRCA2. This work aims to clarify how environmental factors interact with epigenetic regulation to influence breast cancer susceptibility across generations. Identifying DNAm biomarkers linked to exposure and disease risk will advance understanding of transgenerational inheritance mechanisms and support prevention strategies targeting environmental and chemical risk factors.

Lay Language Abstract: This study examines how exposure to environmental factors, such as chemicals like DDT, during pregnancy may influence breast cancer risk and related health outcomes across multiple generations. By analyzing patterns in DNA methylation—chemical tags that help regulate how genes are turned on or off—we examine whether these changes are shared between mothers and daughters and linked to obesity, age at first menstruation, and breast cancer risk.. Understanding these patterns can help explain how environmental exposures affect long-term health and guide future prevention strategies.

24 TUMOR-RESPONSIVE NANOTHERAPY ENABLES DURABLE IMMUNITY IN COLD BLADDER CANCERS

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Although immune checkpoint blockade has transformed cancer therapy, many solid tumors remain immunologically "cold," lacking sufficient immune infiltration and therefore responding poorly to treatment. Strategies that simultaneously promote tumor destruction and immune activation are needed to overcome this limitation. Here, we developed a tumor-responsive nanotherapy platform that integrates chemotherapy, innate immune stimulation, and checkpoint blockade to coordinate tumor killing with immune activation. The system employs a PVA-porphyrin-catechol nanoparticle (PPCN) to deliver doxorubicin (DOX) and the TLR7/8 agonist R848, combined with systemic anti–PD-1 therapy. In the syngeneic MB49 bladder cancer model, this nanotherapy produced complete tumor regression in treated mice, whereas monotherapies or dual treatments achieved only partial responses. Notably, mice that achieved complete remission resisted tumor rechallenge, demonstrating the establishment of durable antitumor immune memory. Mechanistic analyses revealed that treatment significantly increased intratumoral T-cell infiltration and activation while reducing regulatory T cells. In parallel, therapy induced broad remodeling of tumor-associated myeloid populations, shifting the tumor microenvironment toward a pro-inflammatory state that supports effective antitumor immunity. Together, these findings establish that tumor-responsive nanotherapy can convert immunologically cold tumors into immune-responsive tumors while enabling durable antitumor immunity, providing a promising strategy to overcome resistance to checkpoint blockade.

Lay Language Abstract: While immunotherapy has transformed cancer treatment, many tumors remain invisible to the immune system and fail to respond to these therapies. We developed a nanoparticle-based treatment that delivers chemotherapy and immune-stimulating drugs directly to tumors while also using an immune checkpoint therapy. In a mouse model of bladder cancer, this approach eliminated tumors and

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enabled the immune system to remember and reject the cancer if it returned. By turning immune-silent tumors into immune-active ones, this strategy could help extend the benefits of immunotherapy to more patients.

25 IRON METABOLISM UNDERLIES THE ACTIVATION OF CANCER ASSOCIATED FIBROBLASTS

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Pancreatic ductal adenocarcinoma (PDAC) has one of the highest mortality rates among cancers with a 5-year survival rate of 13%. This malignant disease is characterized by a dense, fibrotic stroma primarily driven by cancer-associated fibroblasts (CAFs). However, little is known about the molecular mechanisms underlying the activation of myofibroblasts/inflammatory CAFs (myCAFs/iCAFs) from pancreatic stellate cells. Our analysis of ATAC-seq conducted on in vitro CAF model cell lines suggests that distinct landscapes of chromatin accessibility may underlie this process. Here, we show that pharmacologic inhibition of the p300/CBP histone acetyltransferase complex suppresses activated CAF morphology, CAF transcriptional signatures, and the growth of tumor organoids in co-culture systems. Interestingly, RNA-seq analysis revealed an upregulation of heme metabolism that coincides with A485 treatment for both myCAFs and iCAFs, suggesting the potential dependency of CAF activation on iron processes. Both iCAFs and myCAFs also showed significantly reduced viability and CAF marker expression upon iron chelation compared with quiescent PSCs, and iron supplementation rescued this phenotype. Together, these findings suggest a link between epigenetics and iron metabolism in the context of CAF activation. Targeting this axis for CAFs in PDAC may therefore serve as a promising strategy to improve therapeutic interventions.

Lay Language Abstract: Pancreatic cancer is hard to treat partly because tumors surround themselves with a thick, scar-like tissue that helps them grow and blocks drugs. This scar tissue is made by fibroblasts that cancer cells recruit and activate, driving them to produce collagen. We found that blocking a key protein that controls gene activity can push these activated fibroblasts back toward a quieter state and slow down tumor growth in lab models. We also found that activated fibroblasts rely more on iron, so removing iron weakens them, suggesting a new way to target the tumor's support system.

26 LABVAX 3(22)–23 PEPTIDE VACCINE PLUS GM-CSF AND PEMBROLIZUMAB IN LABYRINTHIN-EXPRESSING METASTATIC ADENOCARCINOMA: PRELIMINARY PHASE II RESULTS

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Background - Labyrinthin (Lab) is a tumor-specific surface antigen expressed in adenocarcinomas across multiple tumor types. LabVax 3(22)–23 is a novel peptide vaccine composed of four synthetic labyrinthin-derived peptides designed to stimulate both T- and B-cell responses against Lab-expressing tumors. This first-in-human Phase I/II study (UCDCC#296; NCT05101356) evaluates the feasibility, safety, and preliminary

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activity of LabVax in patients with Lab-positive metastatic or recurrent lung adenocarcinoma (LUAD, Cohort A) and other adenocarcinomas (Cohort B) following progression on at least one prior line of anti–PD-(L)1 therapy at the UCDCCC.

Methods - Eligible adult patients with Lab-positive tumors (>5% of tumor cells by immunohistochemistry), ECOG performance status 0–1, and adequate organ function received standard-of-care pembrolizumab with intradermal LabVax vaccination and subcutaneous GM-CSF at weeks 7, 8, 10, 13, and 19. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll density gradient centrifugation and banked for immune profiling using bulk RNA sequencing and multicolor flow cytometry. Serum IgG antibodies against the four vaccine peptides were quantified by ELISA.

Results - In Cohort A, 7 of 11 screened patients with LUAD were enrolled. Median age was 65 years (range 40–82); female/male ratio was 4/3; race distribution was White/Asian/Black 4/2/1; ECOG performance status was 0/1 in 1/6 patients. Patients were heavily pretreated, with a median of four prior lines of systemic therapy (range 2–6). Of 7 patients, 5 evaluable patients received at least three doses of LabVax. Median progression-free survival was 9.7 months (range 4.1–10.5) with a median follow-up of 14.2 months (range 10.3–21.4). By RECIST v1.1, one patient achieved a partial response and four had stable disease after vaccination, yielding an objective response rate of 20%. Preliminary analyses demonstrated the activation of T-cell and B-cell responses, with detectable serum anti-Labyrinthin IgG antibodies in patients receiving LabVax alone and in combination with pembrolizumab. Additional analyses of Cohort A are ongoing.

Conclusion - Treatment with LabVax 3(22)–23 plus GM-CSF and pembrolizumab was safe and well tolerated, generating measurable immune responses and encouraging clinical activity in heavily pretreated patients with Lab-expressing LUAD. These preliminary findings support further evaluation of Lab-targeted vaccination strategies in LUAD.

Lay Language Abstract: Our research studies a new cancer vaccine ("LabVax 3(22)–23") designed to help the immune system better recognize and attack certain types of cancer. The vaccine targets a protein called Labyrinthin, which is found on many adenocarcinomas, including lung cancer, but not on most normal cells. In a phase II clinical trial at the UC Davis Comprehensive Cancer Center, we combined this vaccine with the immunotherapy drug pembrolizumab to see whether it could safely stimulate the immune system in patients whose cancer had already progressed on prior treatments. Early results suggest the vaccine can activate immune responses and may help stabilize or shrink tumors in some patients. These findings support further research into cancer vaccines as a potential new treatment approach for advanced cancers.

27 BRD2 UPREGULATION AS AN ADAPTIVE RESISTANCE MECHANISM TO BET INHIBITION IN PAN-CANCER

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Bromodomain and extra-terminal (BET) proteins are a family of four members: BRD2, BRD3, BRD4 and BRDT. These proteins are epigenetic readers, binding to acetylated lysine residues on histones. BET proteins are often dysregulated and drive oncogene transcription across various cancers. Given their critical role in transcriptional regulation, they have emerged as promising therapeutic targets for small-molecule BET inhibitors (BETi), including JQ1. Despite promising preclinical results and ongoing BETi clinical trials, their

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therapeutic efficacy has been hindered by adaptive resistance. However, the mechanisms underlying this resistance remain largely unknown. Our RNA-seq analysis revealed significant upregulation of BRD2 upon JQ1 treatment in pancreatic (PDAC) cell lines. Further bioinformatic analysis of public RNA-seq data equally showed upregulation of BRD2 upon treatment across cancer types, suggesting BRD2 may mediate adaptive resistance to BET inhibition in pan-cancer. Additionally, this upregulation was observed in leukemia, glioblastoma, lung, and breast cancer at the protein level. Functional studies confirmed BRD2 depletion sensitized many cancer cell types to JQ1 in vitro and PDAC cells in vivo. This suggests that BRD2 upregulation plays a conserved role in resistance mechanisms, potentially conferring a survival advantage to cancer cells. These results highlight BRD2 as a key factor in BET inhibitor resistance and inform the development of strategies to enhance the clinical impact of BET inhibitors in cancer therapeutics.

Lay Language Abstract: BET proteins help control which genes are turned on in cells, and when they are dysregulated they can drive cancer growth. Drugs called BET inhibitors were developed to block these proteins, but many cancers become resistant to them. Our research found that cancer cells increase levels of one BET protein, BRD2, after treatment, which may help them survive. Understanding this resistance could help improve future cancer therapies.

28 DESIGN AND DEVELOPMENT OF A PHANTOM FOR MODELING HEPATIC ARTERY BLOOD FLOW

Vinay Jain, Undergraduate Student[1], *Brahim Mehadji*[2,3], *Emilie Roncali*[1,3]
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Current intra-arterial treatments for liver cancer using microspheres face challenges in accurately predicting drug distribution within the organ's vascular system. Computational fluid dynamics (CFD) simulations can help model blood flow within arterial trees to optimize treatment planning; however, these techniques are difficult to implement accurately without physical validation. To date, no phantom exists that can mimic liver perfusion. To address this gap, we designed and fabricated a realistic 3D model of the human hepatic arterial system. This phantom enables direct visualization and quantitative analysis of flow using perfusion computed tomography (CT). Perfusion CT allows visualization of blood transport by tracking the temporal evolution of a contrast agent within the 3D-printed porous vasculature through repeated imaging at short time intervals. The vasculature, designed with anatomically realistic dimensions and proportions, is embedded in foam to mimic arterial blood supply within liver parenchyma. A peristaltic pump drives fluid circulation within a closed-loop system that feeds the phantom vasculature, simulating physiologic flow conditions. Experiments are performed using the EXPLORER scanner. An iodine-based contrast agent is administered as a bolus injection into the inlet tubing connected to the phantom, and its propagation through the vasculature is visualized using dynamic CT imaging.

Lay Language Abstract: Doctors treat liver cancer by sending drug-filled microbeads through the organ's blood vessels, but predicting exactly where these drugs will end up is incredibly difficult. While computer simulations can help map this blood flow to improve therapies, they are essentially educated guesses that must be verified against a physical model. Since no realistic physical model—or medical "phantom"—of a living human liver existed, we built one. We created a highly realistic, 3D-printed network of liver blood vessels and attached a mechanical pump to push fluid through it, mimicking the natural rhythm of a heartbeat. By injecting a medical dye and scanning the model with an advanced CT machine, we can watch how fluids travel through the system

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in real-time. This gives researchers a hands-on way to prove their computer simulations are accurate, ultimately leading to much more precise and effective cancer treatments.

29 THE TUMOR MICROENVIRONMENT INFORMS ANTI-PD-1 CHECKPOINT THERAPY EFFICACY IN AGED MICE WITH TNBC

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[1]Department of Orthopaedic Surgery, UC Davis, Sacramento, CA; [2]UC Davis Comprehensive Cancer Center, Sacramento, CA

Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by highly aggressive tumorigenesis and poor survival rates. TNBC also demonstrates relatively high immune infiltration due to its high tumor mutational burden making it susceptible to immune checkpoint therapy (ICT), such as anti-PD-1. However, ICT success has been relatively limited in TNBC (ORR ~18-20%) which could be due to a cold tumor microenvironment (TME). Thus, to elucidate the contribution of the TME to anti-PD-1 therapy efficacy, E0771 GFP/Luc TNBC cells were orthotopically implanted into aged (>21-month-old) female C57BL/6 mice. Tumor growth and in-vivo imaging to track metastasis was assessed 2x/week. When tumors reached 300 mm3, anti-PD-1 therapy (5 mg/kg) was initiated 2x/week up to humane end points. Primary and metastatic tumors were collected for immunofluorescence, flow cytometry, and single cell RNA sequencing to compare immune and stromal populations between anti-PD-1 responders, non-responders and isotype-treated mice.
Anti-PD-1 therapy significantly decreased tumor volume compared to isotype-control. Immunofluorescence revealed that anti-PD-1 responders showcase a hot TME consisting of a greater percentage of CD8+ T cells within the core of the tumor, a greater percentage of F4/80 macrophages, less cancer-associated fibroblasts (CAFs), less CAF-derived immunosuppressive ECM molecules, and less T-regulatory cells, as well as less T-cell exhaustion. Flow cytometry illustrated that anti-PD-1 responders have less FOXP3+ T-regs whereas non-responders showcase less CD4+ T-helper cells and CD86+ macrophages, and more Ly6G+ polymorphonuclear myeloid derived suppressor cells. ScRNA-seq revealed an upregulation in genes related to immune cell function, apoptosis and tumor suppression, and immunological memory and a downregulation of genes related to the cell cycle, immune checkpoints, and tumor progression in anti-PD-1 responders. These findings indicate that the TME can affect ICT efficacy in an aged population. Additional studies are in progress to identify age-dependent differences in response to ICT to inform clinicians of potential novel treatment regimens with existing therapeutics for women with TNBC.

Lay Language Abstract: Breast cancer is one of the leading causes of cancer death among women. Immune checkpoint therapy, such as anti-PD-1 has become the standard treatment for patients with various types of cancer and has significantly improved survival rates. Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by highly aggressive tumorigenesis and poor survival rates, but it is also the subtype of breast cancer that demonstrates the greatest degree of immune infiltration enabling the use of immune checkpoint therapy for treatment of TNBC. Nonetheless, immune checkpoint therapy success has been relatively limited in TNBC. We sought to determine how the tumor microenvironment can predict anti-PD-1 therapy efficacy in aged female mice with TNBC to inform novel treatment strategies for women with TNBC based on immune and stromal composition of tumors.

30 GUT MICROBIOTA–MEDIATED COLONIC PROSTAGLANDIN METABOLISM IN COLORECTAL CANCER

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Prostaglandins (PGs) are bioactive lipid mediators that play critical roles in inflammation and cancer. Elevated PG levels are a hallmark of many malignancies, including colorectal cancer (CRC), and cyclooxygenase (COX) inhibitors such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most effective agents for CRC prevention. However, studies of PG biology have largely focused on host biosynthetic pathways, while the contribution of gut microbiota to PG metabolism remains poorly understood.
Here, we identify a distinct, microbiota-dependent pathway in the colon in which gut microbes directly regulate PG metabolism and elevate colonic PG levels. Conventionally raised mice exhibit significantly higher concentrations of multiple PG species in the colon compared to germ-free mice. This effect is mediated by bacterial β-glucuronidases (GUS), which deconjugate host-derived PG glucuronides—less active or inactive metabolites—to regenerate bioactive free-form PGs. Consistent with this mechanism, administration of purified GUS enzyme or colonization with GUS-expressing bacteria increases colonic PG levels in germ-free mice. Together, these findings uncover a previously unrecognized role for gut microbiota in colonic PG metabolism and provide mechanistic insight into how microbial enzymatic activity shapes host inflammatory signaling and contributes to CRC progression.

Lay Language Abstract: Prostaglandins are natural chemical messengers in the body that help control inflammation and are closely linked to cancer risk. While these molecules are made by our own cells, we discovered that gut bacteria can also modify them in the colon, increasing their activity. Our research shows that certain bacterial enzymes can "reactivate" prostaglandins that the body has already processed, leading to higher levels in the gut. This finding reveals a new way in which gut microbes influence inflammation and may help explain how the microbiome contributes to colorectal cancer.

31 HIGH AFFINITY IL-15RA EXPRESSION DEFINES A PD-L1-ENRICHED IMMUNOSUPPRESSIVE MYELOID POPULATION IN HUMAN SARCOMA

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Background: Interleukin-15 (IL-15) is classically associated with anti-tumor immunity through stimulation of NK cells and T cells, and IL-15 agonists are under active clinical investigation in oncology. We have observed an unexpected pro-tumorigenic effect of IL-15 through promotion of suppressive functions of myeloid-derived

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suppressor cells (MDSCs). We sought to evaluate the association of IL-15 receptor alpha (IL-15Rα) expression on myeloid populations with immunosuppressive phenotypes in a cohort of sarcoma patients from February 2025 to January 2026.

Methods: Paired peripheral blood and tumor samples were collected from 19 soft tissue sarcoma patients (median age 63 years, 63% female, 84% AJCC stage III, 79% high grade; 17 paired, 2 blood-only). Multiparameter flow cytometry compared IL-15Rα+ versus IL-15Rα− subsets across PMN-MDSCs, monocytes/TAMs, and M-MDSCs. Expression of immunosuppressive markers PD-L1, LOX-1, B7-H3, CD206, and ARG1 were quantified. Serum IL-6 levels were correlated with IL-15Rα+ frequencies.

Results: IL-15Rα+ myeloid cells were significantly enriched in tumors compared to blood for monocytes/TAMs (median 3.9% to 58.8%, p=0.003) and M-MDSCs (4.0% to 20.3%, p=0.017). PD-L1 was significantly elevated on IL-15Rα+ cells across all three myeloid populations in both blood and tumor (p<0.001 to p=0.026). LOX-1 was significantly higher on IL-15Rα+ cells in 5 of 6 myeloid population comparisons. Serum IL-6 showed a significant negative correlation with IL-15Rα+ M-MDSC frequency in blood (r=−0.51, p=0.036, n=17). Tumor PMN-MDSC frequency inversely correlated with T cell (r=−0.78, p=0.001) and NK cell infiltration (r=−0.68, p=0.008), and TAM frequency inversely correlated with NK cells (r=−0.74, p=0.002), suggesting myeloid expansion displaces effector lymphocytes.

Discussion: IL-15Rα marks a PD-L1-high immunosuppressive myeloid subset that accumulates in the sarcoma tumor microenvironment. The inverse relationship between myeloid and effector cell frequencies supports functional immunosuppression. These findings suggest that IL-15 agonist therapies may inadvertently expand suppressive myeloid populations, providing rationale for combination strategies with MDSC-targeting therapies.

Lay Language Abstract: Our immune system has natural killer cells and T cells that fight cancer. A protein called IL-15 is being developed as a cancer therapy to boost these cancer-fighting cells. However, we discovered that IL-15 may also activate harmful immune cells called MDSCs that actually protect tumors from being destroyed. In sarcoma patients, we found that tumors with more of these harmful cells had fewer cancer-fighting cells. Understanding this dual effect is critical for designing better immunotherapy combinations for sarcoma patients.

32 BIOMARKER-BASED CHARACTERIZATION OF CANINE HEPATOCELLULAR CARCINOMA (HCC) AS A NATURAL ANIMAL MODEL FOR HUMAN HCC

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Hepatocellular carcinoma (HCC) accounts for approximately 75–85% of primary liver cancers in humans. In dogs, HCC is the most common primary liver malignancy, comprising 35–60% of all hepatic tumors. Canine HCC offers a spontaneously occurring and clinically relevant model for studying human HCC. However, the molecular and immunological landscape of canine HCC remains insufficiently defined. This study aims to characterize canine HCC to identify biomarkers and explore therapeutic targets applicable to both veterinary and human HCC. Samples were obtained from client-owned dogs (n=14) diagnosed with HCC who underwent surgical resection at the UC Davis Veterinary Medical Hospital. For each case, paired tumor and adjacent non-tumor liver tissues, as well as plasma, were collected. Additionally, plasma samples from age- and sex-

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matched healthy control dogs (n =14) were included for comparative analysis. Characterization of HCC was conducted using radiology (CT Scans), histopathology, immunohistochemistry (IHC) for Galectin-1, cytokine profiling, transcriptomics, proteomics, and untargeted metabolomics. Histopathologic evaluation demonstrated loss of normal hepatic architecture and evidence of malignant cells. IHC confirmed upregulation of Galectin-1 expression (cancer marker) in tumor vs non-tumor tissue. Transcriptomic analysis in canine HCC revealed upregulation of pathways associated with tumor metabolism, proliferation, intracellular signaling, and inflammatory regulation. Downregulated pathways included those related to normal hepatic function, xenobiotic metabolism and homeostatic immune responses. Proteomic profiling revealed profiles of proteins associated with cancer in general, and seventeen genes were upregulated at both the transcription and protein level (fold change >2, $p<0.05$) in particular. Metabolomics demonstrated distinct metabolic profiles associated with energy metabolism in tumor tissue. These findings support the utility of canine HCC as a relevant comparative model for human HCC. The integration of the above multimodality analysis of HCC by machine learning (ML) is under way. ML analysis may enhance our understanding of HCC pathogenesis, improve diagnosis and prognosis, and may help identify new targets for drug development.

33 EVALUATION OF NIMBOLIDE AS A TARGETED THERAPY FOR BLADDER CANCER

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Non-muscle-invasive bladder cancer (NMIBC) is among the most commonly diagnosed malignancies in the United States. Despite initial transurethral resection of the bladder tumor (TURBT) and subsequent intravesical therapies, many patients experience significant toxicity or eventual relapse. These limitations demonstrate the need for safer and more effective therapies that target both the cancer cells and the surrounding tumor microenvironment. Here, we characterized the therapeutic potential and molecular mechanism of nimbolide, a neem (Azadirachta indica)-derived limonoid. This characterization was performed using both human NMIBC (hNMIBC) cell lines and patient-derived 3D-printed tumoroids with immune co-culture.

Dose-response analyses demonstrated that nimbolide induced significant reduction of hNMIBC viability. Cytotoxicity assays further showed that these effects are specific to malignant cells, as nimbolide exhibited reduced toxicity towards non-cancerous bladder fibroblasts in comparison. In co-culture experiments with peripheral blood mononuclear cells (PBMCs), nimbolide also increased immune cell engagement and infiltration, indicating immunomodulatory effects.

Using a physiologically relevant recapitulated tumor microenvironment, both nimoblide and standard chemotherapeutic agents were tested and compared in patient-derived, 3D bladder cancer tumoroids. Nimbolide treatment produced significant tumor growth inhibition suggesting promising translational potential. Through mechanistic analyses in vitro, we demonstrated that nimbolide significantly upregulated expression and mitochondrial localization of heme oxygenase-1 (HMOX1), an enzyme responsible for the degradation of heme into biliverdin, carbon monoxide, and ferrous iron. This reaction leads to increased intracellular iron levels which further react with hydrogen peroxide to produce reactive oxygen species (ROS). Increased ROS damages the cell membrane via lipid peroxidation and leads to ferroptotic cell death. Additionally, ROS leads to further HMOX1 induction, creating a self-amplified death loop, often indicated by increased MitoSOX, mitochondrial fragmentation, and DRP1 activation.

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These findings position nimbolide as a potent inducer of mitochondrial iron-dependent ferroptosis in bladder cancer, shifting HMOX1 from a cytoprotective mediator to a pro-death effector under conditions of sustained oxidative and iron stress. By integrating metabolic disruption with microenvironment-relevant models, this study suggests that nimbolide could be a promising alternative treatment for NMIBC through the induction of ferroptosis. Current efforts are directed toward exploring the structure-activity relations (SAR) of nimbolide derivatives to guide future optimization.

Lay Language Abstract: Our research investigates nimbolide, a bioactive compound derived from the neem tree as a potential treatment for non-muscle-invasive bladder cancer. Using human cancer cells and patient-derived 3D tumor models that mimic the tumor micro environment, we found that nimbolide selectively suppresses bladder cancer growth while showing lower toxicity toward normal cells. Mechanistically, nimbolide disrupts cellular iron regulation and increases oxidative stress, triggering a form of cancer cell death called ferroptosis. It also enhances interactions between tumor cells and immune cells, suggesting a potential role in strengthening anti-tumor immune responses. These findings highlight nimbolide as a promising candidate for developing new therapies for bladder cancer.

34 A RAT GLIOMA SPHEROID-NEURAL CELL TRI-CULTURE MODEL TO INVESTIGATE CELLULAR CROSSTALK IN GLIOMA PATHOLOGY

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Introduction Glioblastoma is one of the most lethal primary brain tumors in adults, characterized by diffuse cellular infiltration into the brain parenchyma and high recurrence rates. Although glioblastoma progression has traditionally been attributed to tumor-intrinsic mechanisms, increasing evidence highlights the critical role of crosstalk between tumor cells and surrounding neural and immune cells in driving disease pathology. However, most in vitro models fail to recapitulate this multicellular complexity due to the challenges of maintaining multiple interacting cell types under physiologically-relevant conditions. To address this gap, we developed a cell culture model, in which a C6 rat glioma spheroid is integrated with primary rat neurons, astrocytes, and microglia under serum-free conditions. This platform enables the investigation of glioma pathology within a multicellular neural–immune tumor context. Using this model, we examined how tumor–microglia interactions regulate glioma spheroid growth and invasion, as well as microglial proliferation and morphological changes.

Materials and Methods Tri-cultures were established from dissociated neonatal rat cortical cells maintained under the specific growth medium, consisting of IL-34, TGF-β, and cholesterol that are essential for microglial survival and function. GFP-expressing C6 glioma spheroids were generated using agarose-coated plates and integrated into mature tri-cultures at DIV7 to establish the glioma–tri-culture model. Tumor growth and invasion were monitored over 14 days. The cultures were then chemically fixed and immunostained to assess microglial proliferation and morphological evolution of cells.

Results In the presence of microglia, glioma spheroids exhibited greater growth, whereas no significant difference was observed in the extent of spheroid spread. Conversely, microglia numbers were higher in the vicinity of the glioma spheroid with microglia exhibiting more ramification compared to microglia distal to the spheroid.

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Future directions Beyond tumor–microglia interactions, this platform provides a unique opportunity to interrogate glioma–neuron signaling within a physiologically-relevant multicellular environment. Future work will investigate neuronal activity-dependent tumor modulation and tumor-induced neuronal remodeling to further define the integrated tumor–neural–immune axis.

Lay Language Abstract: We developed an in vitro brain tumor model that includes four pathologically relevant cell types–glioma cells, neurons, astrocytes, and microglia–to investigate how their interactions influence its physiology. . Using this platform, we observed significant physiological changes in both tumor and immune cells when they were cultured together. Moreover, this model provides a unique environment to study the complex "neural–immune–tumor axis" and identify new targets for brain cancer treatment.

35 ASSESSING THE ROLE OF GLP-1 AGONISTS IN MITIGATING AROMATASE INHIBITOR–INDUCED BONE LOSS IN BREAST CANCER PATIENTS

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Aromatase inhibitors (AI) are a common adjuvant treatment for hormone receptor positive breast cancer. In reducing residual estrogen production, AI are associated with a two to four-fold increase in bone loss in postmenopausal women, which may only be partly reversible after discontinuation. With patients living longer with breast cancer, this adverse effect is well known and challenging to prevent and treat. Glucagon-like peptide-1 receptor (GLP1) agonists have increasingly grown in use as treatment for patients with type 2 diabetes mellitus (T2DM) and obesity, and are thought to improve bone health through multiple mechanisms. However, heterogeneity between human studies affects conclusions that can be drawn on bone formation. Given the increasing use of GLP1 agonists and a physiological basis for improvement in bone health similar to that of estrogen, this study aims to address whether these agents can prevent loss of bone mineral density (BMD) in postmenopausal women on adjuvant therapy for hormone receptor-positive breast cancer.

This retrospective chart review will include postmenopausal women treated between June 2021 and December 2025 at a single institution. Eligible patients will be ≥60 years old with stage I–III hormone receptor–positive, HER2-negative breast cancer who are receiving adjuvant AI therapy (anastrozole, letrozole, or exemestane) for at least 1 year. The exposure group will include patients treated with simultaneous GLP-1 receptor agonist for at least 6 months, while the control group will include patients not receiving GLP-1 but who may be receiving other antidiabetic medications. Patients with baseline osteoporosis, prior fragility fracture, active smoking, prolonged glucocorticoid or proton pump inhibitor use, endocrine disorders affecting bone metabolism, metastatic disease, or prior osteoporosis treatment will be excluded.

The primary outcome will be change in lumbar spine BMD from baseline to 2 and 4 years after AI initiation. Additional primary outcomes include the proportion of patients diagnosed with osteoporosis and time to osteoporosis diagnosis. Analyses will include stratification by diabetes status and multivariable regression to adjust for potential confounders.

If a protective association is observed, GLP-1 therapy may represent a potential strategy to reduce osteoporosis risk in postmenopausal patients undergoing endocrine therapy for breast cancer.

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Lay Language Abstract: Aromatase inhibitors are commonly used to treat hormone receptor–positive breast cancer in postmenopausal women, but they can also cause significant bone loss and increase the risk of osteoporosis. Glucagon-like peptide-1 (GLP-1) receptor agonists, medications widely used to treat diabetes and obesity, may have beneficial effects on bone health. This study will examine whether women taking GLP-1 medications while receiving aromatase inhibitor therapy experience less bone loss than those who are not taking these medications. Understanding this relationship could help identify new ways to reduce osteoporosis risk and improve long-term health for breast cancer survivors.

36 A PHASE I/IB STUDY OF CAPMATINIB PLUS TRAMETINIB IN PATIENTS WITH METASTATIC MET EXON 14 SKIPPING MUTATION POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

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Introduction: MET tyrosine kinase (TKI) therapy has improved outcomes in patients with non-small cell lung cancer (NSCLC) harboring MET exon 14 (METex14) skipping mutations. However, primary and acquired resistance ultimately limits durability of response. Clinical genomics has identified frequent co-mutations in the MAPK signaling pathway in METex14 NSCLC. In preclinical models, hyperactivation of MAPK signaling promoted MET TKI resistance in MET exon 14 preclinical models and co-treatment with a MET and MEK inhibitor overcame this resistance. This study evaluated the safety and efficacy of capmatinib with trametinib in patients with advanced (stage IIIB/IV) METex14 NSCLC who had progressed on prior treatment with at least one MET inhibitor.

Methods: A multicenter phase I study evaluated capmatinib in combination with trametinib in patients with advanced stage NSCLC harboring METex14 skipping mutations and prior exposure to at least one MET TKI. A 3+3 dose-escalation design was employed to assess safety and tolerability. Two dose levels were investigated, level 1: capmatinib 300 mg PO twice daily plus trametinib 1.5 mg PO daily and level 2: capmatinib 400 mg PO twice daily plus trametinib 1.5 mg PO daily. The primary endpoint was to determine the safety and tolerability.

Results: Three patients (n = 3) were enrolled in the study and completed a median of 3 cycles of therapy. Dose-limiting toxicities, including rash, edema, and nausea, necessitated dose reduction in the first two patients and initiation of the third patient at a lower dose level. Ultimately, all patients discontinued therapy because of treatment related adverse events.

Conclusions: In this phase I trial, the combination of MET and MEK inhibitors with capmatinib and trametinib was associated with clinically significant treatment related adverse events and DLTs that resulted in discontinuation of therapy in all participants. Further investigation would require alternative dosing strategies or different combinations to improve tolerability in this patient population.

Lay Language Abstract: This project showed that combination targeted therapy (trametinib + capmatinib) for non-small cell lung cancer patients may have untoward adverse effects which may limit their tolerability.

37 UNDERSTANDING THE CANCER SCREENING GAP AMONG CALIFORNIA FIREFIGHTERS

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Introduction. Cancer burden in firefighters is high. Early detection through cancer screening significantly reduces cancer-specific mortality by identifying cancer at earlier stages when curative interventions have optimal efficacy. The uptake of cancer screening among firefighters remains poorly characterized, with limited data on screening prevalence and factors that predict screening behavior in this high-risk occupational population.

Methods. The California Firefighter Cancer Research Study (CAFF-CRS) assessed cancer screening behavior from 2,184 firefighter participants across California using self-reported surveys. Participants were asked to report on cancer screening for breast, cervical, colorectal, lung, prostate, and skin cancer. Screening compliances were evaluated according to two established guidelines among those eligible: (1) the U.S. Preventive Services Task Force (USPSTF), and (2) the National Fire Protection Association (NFPA) 1582 Standard on Comprehensive Occupational Medical Programs for Fire Departments (2022 edition).

Results. USPSTF screening compliance was 57% for colorectal cancer, 69% for breast cancer, 61% for cervical cancer, 5% for lung cancer, and 66% for prostate cancer. For colorectal cancer, compliance with USPSTF increased significantly with increasing age (OR=1.14; 95% CI=1.10–1.20, for each year of age), increasing years of service (OR=1.04, 95% CI=1.01-1.07, for each year of service. Additionally, screening compliance decreased with time, since routine check-ups with a doctor were higher among firefighters with a diagnosis of a chronic condition requiring treatment (e.g., diabetes, high cholesterol, etc.) and among those with a family history of cancer who discussed it with their providers. For prostate cancer, compliance with USPSTF increased significantly with increasing age (OR=1.55; 95% CI=1.17–2.25, for each year of age), and increasing years of service (OR=1.07, 95% CI=1.00-1.16, for each year of service). Additionally, screening compliance was higher for participants who were aware of USPSTF guidelines for cancer screening (OR=6.68, 95% CI=1.27–123.32). Compliance patterns were similar when assessing NFPA guidelines, which typically recommend starting cancer screening at younger ages. Skin cancer screening compliance with NFPA showed many of the same patterns of association as colorectal and prostate cancer screening.

Conclusions. These findings suggest that some groups of firefighters may need more targeted education regarding the importance of cancer screening.

Lay Language Abstract: Early detection through cancer screening is especially important for firefighters, who experience a high burden of cancer. In this study, we looked at how often firefighters in California report getting recommended cancer screenings, such as for skin, colorectal, lung, and prostate cancer. By comparing their screening habits with national and occupational health guidelines, we hope to identify gaps and highlight where better education and outreach could help protect firefighters' long-term health.

38 COMBINED IMMUNE CHECKPOINT BLOCKADE AND CUPROPTOSIS INDUCTION ENHANCES CYTOTOXIC LYMPHOCYTE INFILTRATION AND ACTIVATION IN OSCC

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Oral squamous cell carcinoma (OSCC) is the seventh most common cancer worldwide and exhibits profound resistance to immune checkpoint blockade. Despite the success of anti-PD-1/PD-L1 therapies in other malignancies, only ~20% of patients with recurrent/metastatic OSCC achieve durable clinical benefit, suggesting that intrinsic features of the tumor microenvironment (TME) limit effective anti-tumor immunity. Identifying therapeutic strategies that increase tumor immunogenicity and promote cytotoxic immune engagement remains a critical challenge. Cuproptosis is a recently described copper-dependent form of regulated cell death induced by intracellular copper accumulation, disrupting lipoylated TCA cycle proteins. Emerging evidence suggests that the resulting metabolic stress and cell death may trigger the release of damage-associated molecular patterns (DAMPs) that serve as immunogenic cues within the TME. While the cuproptosis-inducer elesclomol complexed with $CuCl_2$ (eles-Cu) has demonstrated anti-tumor activity in select cancer models, its ability to modulate anti-tumor immunity in immunotherapy-resistant cancers such as OSCC remains undefined. Using an immunocompetent syngeneic murine SCC model, we evaluated whether cuproptosis induction enhances the efficacy of anti-PD-L1 immune checkpoint inhibition. Combination treatment with eles-Cu and anti-PD-L1 significantly reduced tumor growth and increased complete tumor regression relative to either monotherapy (37.5% dual vs. 10% anti-PD-L1 vs. 0% eles-Cu). To define the immunologic correlates of this response, tumors were analyzed at an early timepoint using OPAL multiplex immunohistochemistry. Dual-treated tumors demonstrated increased infiltration of $CD8\alpha^+$ T cells and $NK1.1^+$ natural killer cells, accompanied by elevated granzyme B expression, indicating enhanced cytotoxic activation. Importantly, stratification of tumor core vs edge revealed increased immune penetration into the tumor core, a region typically associated with immune exclusion. To explore underlying mechanisms, bulk RNA-seq of eles-Cu–treated SCC cells in vitro revealed significant enrichment of GO terms including 'adaptive immune response' and 'T cell activation' (eles-Cu vs. vehicle). Together, these data position cuproptosis induction as a novel strategy to overcome immune exclusion and sensitize immunotherapy-resistant OSCC to checkpoint blockade. Ongoing studies investigate the mechanisms linking cuproptosis and adaptive anti-tumor immunity, with a focus on tumor-intrinsic antigen presentation and DAMP-mediated immune priming. (This study was funded by CO HNC SPORE P50 CA261605)

Lay Language Abstract: Head and neck cancers, including oral cancer, are difficult to treat because they often stop responding to modern immunotherapy drugs that help the immune system fight tumors. We are investigating a novel approach that uses a copper-based compound to trigger a recently discovered form of cancer cell death called cuproptosis, which we believe may send "danger signals" that activate the immune system. In mouse models of oral cancer, combining this copper compound with immunotherapy dramatically shrank tumors and eliminated them entirely in more animals than either treatment alone. We also found that this combination drove immune cells deeper into the tumor, a major barrier in cancer treatment, suggesting that cuproptosis may physically reshape the tumor environment to allow a stronger immune attack. These findings lay the groundwork for a new strategy to make immunotherapy work for patients whose cancers currently do not respond to it.

39 PULMONARY SARCOMATOID CARCINOMA HARBORING MET EXON 14 SKIPPING MUTATIONS AND HIGH PD-L1 EXPRESSION: CLINICAL OUTCOMES FROM A CASE SERIES

Ralph de Vere White Symposium for Early Stage Investigators in Cancer

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Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare and highly aggressive subtype of non–small cell lung cancer (NSCLC) that is relatively resistant to platinum-based chemotherapy. PSC frequently exhibits high programmed death-ligand 1 (PD-L1) expression and actionable genomic alterations, most commonly mesenchymal–epithelial transition exon 14 skipping mutations (METex14). However, optimal treatment strategies for PSC in the modern therapeutic era remain unclear due to limited clinical data.

Methods: We describe 3 patients with resectable PSC harboring METex14 mutations and high PD-L1 expression recently treated at our institution. Their clinical characteristics and outcomes were compared with 40 NSCLC patients with METex14 mutations treated at our institution.

Results: Case 1: A 71-year-old female with stage IIB (pT3N0) PSC received neoadjuvant capmatinib for 2 weeks while waiting for surgery with initial response followed by surgical resection. She developed rapid postoperative progression while receiving adjuvant capmatinib and later pembrolizumab and subsequently died of disease.

Case 2: An 80-year-old male with stage IIA PSC received neoadjuvant nivolumab plus carboplatin/paclitaxel. Surgery was deferred due to functional decline and complications following endobronchial ultrasound. The patient subsequently received definitive chemoradiation but developed acute hypoxic respiratory failure attributed to Pneumocystis jirovecii pneumonia versus immune-related pneumonitis. Despite treatment with corticosteroids, intravenous immunoglobulin, and trimethoprim–sulfamethoxazole, the patient died after transition to hospice care.

Case 3: A 73-year-old male with stage IIIA PSC received neoadjuvant nivolumab with carboplatin/paclitaxel followed by surgical resection. He remains progression-free at 11 months while receiving adjuvant nivolumab. Single-cell transcriptomic analysis of paired primary tumor and nodal specimens revealed MET, CHEK2, MAP2K mutations with high PD-L1 expression and AE1/AE3 positivity.
Compared with NSCLC patients harboring METex14 mutations, PSC patients demonstrated poorer clinical outcomes and limited responses to both MET-targeted therapy and PD-(L)1–based immunotherapy.

Conclusions: PSC remains a highly aggressive malignancy with poor clinical outcomes. Multidisciplinary and combined-modality treatment strategies warrant further investigation to improve outcomes in PSC.

Lay Language Abstract: Pulmonary sarcomatoid carcinoma (PSC) is a rare and highly aggressive subtype of non–small cell lung cancer (NSCLC). Patients have poorer outcomes in part due to relative resistent to traditional platinum-based chemotherapies. Due to its low incidence, PSC does not have guideline directed management. We highlight three cases of patients with PSC that show the challenges of treatment and shed light on potential treatment strategies.

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40 PATTERNS OF NEOADJUVANT CHEMOTHERAPY (NAC) USE IN STAGE II-III BLADDER CANCER: A CALIFORNIA CANCER REGISTRY (CCR) ANALYSIS

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Background: NAC followed by radical cystectomy (RC) improves survival compared to RC alone in patients with muscle invasive bladder cancer (MIBC), yet real-world uptake has lagged. Adjuvant chemotherapy (AC) for those not receiving NAC has been employed though survival benefit has not been established. With evolving perioperative regimens involving immunotherapy changing the treatment landscape, understanding patterns of treatment over time is important.

Methods: We evaluated patients with Stage II-III bladder cancer aged > 20, diagnosed from 2004-2022 in the CCR, who underwent RC to assess receipt of both systemic and surgical treatment. Descriptive statistics summarized characteristics of the study population by receipt of NAC + RC, RC + AC, or RC alone among patients. Multivariable logistic regression models identified factors associated with receipt of NAC + RC vs those receiving either RC + AC or RC alone.

Results: Among 6749 eligible patients, 2724 (40.4%) received NAC + RC, 438 (6.5%) received RC + AC, and 3587 (53.1%) underwent RC alone. Receipt of NAC was significantly associated with more recent diagnosis (2014-2022 vs 2004-2013): odds ratio [OR] 7.50, 95% CI 6.6.3-8.48), higher neighborhood socioeconomic status (SES) (OR 1.33, 95% CI 1.14-1.56, highest vs lowest tertile), male sex (OR 1.17, 95% CI 1.02-1.34) and care at an NCI-designated Cancer Center (OR 1.40, 95% CI 1.25-1.57). Significantly lower odds of NAC use were observed for those aged > 80 (vs age 20-49; OR 0.31, 95% CI 0.22-0.43), with a Charlson comorbidity score >1 (vs 0, OR: 0.65, 95% CI 0.57-0.75), and Hispanic individuals (vs non-Hispanic White; OR 0.82, 95% CI 0.69-0.99).

Conclusions: NAC use has increased over time, but utilization is lower among older individuals, women, those living in lower SES neighborhoods, Hispanic individuals and those with more comorbidities. These results can help to shape future intervention and optimize treatment utilization as perioperative approaches with broader eligibility criteria emerge.

Lay Language Abstract: Neoadjuvant chemotherapy (chemotherapy given before surgery) followed by surgical removal of the bladder improves survival for patients with muscle-invasive bladder cancer compared to surgery alone. However, real-world use of this approach has not been consistent. Using data from the California Cancer Registry, our study examined patterns of neoadjuvant chemotherapy use among patients diagnosed with Stage II–III bladder cancer between 2004 and 2022 who underwent bladder removal surgery. We found that use of neoadjuvant chemotherapy has increased substantially over time. Despite this progress, neoadjuvant chemotherapy remains less commonly used among certain groups of patients, highlighting ongoing disparities in care.

41 PROOF OF CONCEPT FOR NANOBODY-BASED THERAPY AGAINST OSTEOSARCOMA

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Osteosarcoma (OS) is the most common malignant tumor of the skeletal system. Within these tumors, a small population of cells with stem-like properties, known as cancer stem cells (CSCs), is thought to drive tumor growth and progression. Novel therapeutic strategies such as antibody–drug conjugates (ADCs), which use antibodies to deliver cytotoxic drugs specifically to tumor cells, have been explored for OS but have shown limited efficacy. One possible explanation is the dense extracellular matrix characteristic of osteosarcoma, which can hinder drug penetration, combined with the limited specificity of currently available OS cell-surface markers. Nanobodies represent a promising alternative to conventional antibodies in ADC design because of their much smaller size, which may allow improved tumor penetration. By combining nanobodies with newly identified, highly specific cell surface markers, it may be possible to develop more effective targeted therapies for OS. As a proof of concept, the OS cell line SAOS2 was engineered to express green fluorescent protein (GFP) on the cell membrane, enabling recognition by anti-GFP nanobodies. Co-culture in vitro assays with GFP-labeled and unlabeled tumor cells and an in vivo OS mouse model experiment using wild-type and GFP-labeled tumors were performed to evaluate nanobody targeting of cancer cells. Using patient-derived xenograft (PDX) cell lines and primary tumor samples, we have applied single-cell RNA sequencing to identify cell populations that share features of both tumor cells and bone-forming skeletal lineage populations. Clonal tracking and spatial transcriptomics are further employed to investigate the role of stem cell-like cells in disease development and progression, which altogether could provide a novel framework to prevent OS progression and metastasis.

Lay Language Abstract: Osteosarcoma is a bone tumor that primarily affects young adults and the elderly. Within bone there exists a rare sub population of stem cells called cancer stem cells. Cancer stem cells are important for the growth and metastasis of the tumor. Understanding the properties of cancer stem cells can lead to new understandings on how to create better therapies for osteosarcoma. In the Ambrosi lab we study skeletal stem cells, a rare population of cells in bone that are important for its growth and maintenance. The role of skeletal stem cells in osteosarcoma in unknown and warrants new research.

42 INFLAMMATION AND OCCUPATIONAL EXPOSURES IN THE CALIFORNIA FIREFIGHTER CANCER RESEARCH STUDY (CAFF-CRS) COHORT

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Introduction. Firefighters face several occupational exposures that create a cancer-promoting environment by increasing oxidative stress and chronic inflammation, two mechanistic pathways linking firefighting to increased cancer risk. Little is known regarding which specific occupational factors associate with oxidative stress and inflammation in firefighters.

Methods. Firefighters enrolled in the California Firefighter Cancer Research Study (CAFF-CRS) answered several surveys, participated in health assessments, and provided blood samples that were used to test for 21

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cytokines and chemokines via multiplex Luminex assays, and 87 oxylipins via LC-MS-MS. Multivariate regression models were used to examine the association between occupational factors and biomarker levels in a subset of 247 firefighters enrolled CAFF-CRS.

Results. CAFF-CRS participants had an average of 12.7 (SD=8.7) years of service as a firefighter. Years of service was significantly associated with levels of 13 oxylipins. Levels of 2 anti-inflammatory oxylipins (N-C22:4n6-EA and N-C18:2n6-EA) decreased significantly with increasing years of service, while 11 oxylipins increased significantly with increasing years of service; the strongest positive associations were observed for metabolites of arachidonic acid (5-KETE, 5-HETE, 9-HETE, 8-HETE). Additionally, 5-HETE, 9-HETE, 8-HETE and several other arachidonic acid metabolites were also the oxylipins most significantly associated with PFAS levels, suggesting that arachidonic acid metabolites mediate the association between PFAS and cancer risk in firefighters. Years of service was also significantly associated with 2 cytokines. CXCL10 and CCL2 pro-inflammatory cytokine levels significantly increased with increasing years of service.

Conclusions. These findings may offer insights into the link between biomarkers of exposure and other lifestyle factors that influence cancer risk among firefighters via oxidative stress and inflammation.

Lay Language Abstract: Firefighters face many occupational and lifestyle factors that increase cancer risk. Several of these risk factors are also associated with inflammation, and chronic inflammatory markers have been linked to increased cancer risk. This study examines demographic, occupational, and behavioral characteristics associated with inflammation in a cohort of firefighters enrolled in the California Firefighter Cancer Research Study (CAFF-CRS). We further explore the relationship between immune markers and exposure levels for PFAS and metals measured in blood specimens. These findings offer insight into occupational and behavioral factors as well as environmental contaminants that may influence inflammation and cancer risk among firefighters.

43 MODELING EARLY GASTRIC CANCER EVOLUTION FOLLOWING ARID1A LOSS USING PATIENT-DERIVED GASTRIC ORGANOIDS

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Background: Gastric cancer remains a leading cause of cancer mortality worldwide, with disproportionately worse outcomes among Latino patients in the United States. Despite this burden, Latino populations remain underrepresented in genomic datasets and preclinical models. ARID1A is one of the most frequently mutated tumor suppressor genes in gastric cancer, yet its role in early disease evolution remains incompletely understood. We sought to develop patient-derived gastric organoid models to understand how ARID1A loss contributes to early phenotypic progression.

Methods: Normal gastric organoids were established from Latino patients and engineered using CRISPR/Cas9 to generate isogenic ARID1A/TP53 double-knockout (dKO) and TP53 knockout. Organoids were maintained in long-term culture for up to 350 days. Early (~150 days) and late (~350 days) time points were evaluated using

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histologic changes, RNA sequencing, and whole-exome sequencing to assess phenotypic progression and evolution. Functional assays evaluating proliferation, migration, and drug sensitivities are ongoing.

Results: ARID1A/TP53 dKO organoids exhibited progressive morphological changes and increased proliferative features compared with wild-type controls. RNA sequencing demonstrated time-dependent changes, including suppression of digestion and iron transport pathways and upregulations associated with cilium movement and ciliogenesis. Whole exome sequencing revealed shared mutations across independently derived dKO clones, alongside acquisition of clone-specific variants over time. These alterations involved genes implicated in transcriptional regulation, extracellular matrix remodeling, and receptor signaling, consistent with early genomic instability and divergent clonal evolution.

Conclusions: Patient-derived gastric organoids from Latino individuals demonstrate that combined ARID1A loss drives transcriptional reprogramming and promotes early dysplastic progression. These models establish a translational platform to understand gastric cancer evolution and to identify therapeutic vulnerabilities associated with ARID1A loss. This work provides a mechanistic foundation for drivers of gastric cancer and a platform for precision prevention strategies.

Lay Language Abstract: Gastric (stomach) cancer remains a major cause of cancer deaths worldwide and disproportionately affects Latinos communities, yet these populations are often underrepresented in research studies. Our research investigates how the loss of a gene called ARID1A, which regulates how cells grow and access DNA, may contribute to the earliest stages of stomach cancer. Using Latino patient samples, we were able to generate 3D stomach models and used gene editing to create mutations in the ARID1A gene and study how cells change over time. We found that loss of ARID1A leads to cellular and molecular changes that resemble early cancer development. By better understanding gastric cancer initiation, we may identify new opportunities for early detection, prevention, and targeted treatment of gastric cancer.

44 ESTABLISHING A LINEAGE-TRACED PLATFORM TO STUDY TUMOR-ASSOCIATED MACROPHAGE HETEROGENEITY ACROSS IMMUNOLOGICALLY DISTINCT TUMOR MICROENVIRONMENTS

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Immune checkpoint therapy (ICT) have transformed cancer therapy by enhancing immune recognition and elimination of tumor cells. However, many patients fail to respond because their tumors exhibit poor immune cell infiltration, a state referred to as a “cold” tumor microenvironment (TME) that is unable to mount an effective antitumor immune response. In contrast, “hot” TMEs enriched in immune populations are significantly more responsive to ICT. Although single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have advanced our understanding of TME complexity, key tumor-associated macrophage (TAM) subpopulations remain incompletely defined. Several TAM states have been described, including $SPP1^+$, $TREM2^+$, $MARCO^+$, $FOLR2^+$, and $C1Q^+$ subpopulations, yet their ontogeny, stability, and capacity to transition between functional states, particularly during ICT, remain poorly understood. Distinguishing stable TAM lineages from transient activation states remains a major barrier to therapeutic targeting.

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To address this challenge, we developed a strategy to fluorescently label and enrich tumor-associated myeloid populations using the LysM-Cre; Ai9 (tdTomato) reporter as host for syngeneic triple-negative breast cancer (TNBC) allograft models: E0771 and Py8119; representing relatively “hot” and “cold” TMEs, respectively. Preliminary scRNA-seq analysis of dissociated E0771 tumors identified multiple TME populations, including TAMs, tumor and stromal cells, T/NK cells, B cells, cycling cells, and myeloid-derived suppressor cells (MDSCs). Immune checkpoint gene expression was broadly distributed across these populations, with Pdcd1 (PD-1) enriched in T/NK cells and Cd274 (PD-L1) primarily expressed by myeloid and tumor/stromal compartments. Comparative immune profiling further revealed distinct immunologic landscapes between models. E0771 tumors were enriched for F4/80^{+} TAMs and FOXP3^{+} regulatory T cells, consistent with an inflamed but immunoregulatory TME. In contrast, Py8119 tumors displayed a marked expansion of Ly6G^{+}Ly6C^{-} polymorphonuclear MDSCs despite increased CD8^{+} T cells, supporting their classification as immunologically suppressed. Flow cytometry validated the LysM-Cre; Ai9 system as an effective strategy for labeling tumor-infiltrating myeloid cells, marking 69.7% of F4/80^{+} TAMs and capturing both CD86^{+} (M1-like) and CD206^{+} (M2-like) macrophage states as well as monocytic and PMN-MDSC populations.

Immunofluorescence further confirmed spatial overlap between F4/80^{+} macrophages and tdTomato-labeled cells in tumor tissue. Together, these findings establish LysM-Cre; Ai9 lineage tracing as a robust platform for enriching tumor-associated myeloid populations and enabling high-resolution single-cell analysis of TAM heterogeneity across immunologically distinct TMEs.

Future studies will leverage insights from scRNA-seq and scATAC-seq profiling of lineage-enriched TAM populations that will be used to interrogate a PTEN-deficient TNBC genetically engineered mouse model (GEMM) as well as systematic removal of immune subpopulation during tumorigenesis to hone in to the subpopulations that are immunesuppresive and can be targeted to enhance the efficacy of ICT.

Lay Language Abstract: Immune checkpoint therapy works by helping the immune system recognize and destroy tumor cells, but many tumors avoid this attack by creating an environment that blocks immune activity. Our research studies a type of immune cell called macrophages that can either support or suppress the body’s ability to fight cancer. Using mouse models and advanced genetic technologies, we track and analyze these cells within tumors to understand why some cancers respond to immunotherapy while others do not. By identifying the immune cell populations that control this process, we hope to develop strategies that make resistant tumors more responsive to treatment.

45 OCCUPATIONAL PFAS EXPOSURE AND CARDIOMETABOLIC RISK IN FIREFIGHTERS: IMPLICATIONS FOR CANCER RISK

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Background: Cardiometabolic diseases, including diabetes, hypercholesterolemia, and hypertension, are associated with an increased risk of multiple cancer types. Firefighters experience a higher prevalence of these cardiometabolic risk factors due to their occupational exposures. The National Academies (NASEM) determined in their 2022 report that sufficient evidence exists to link Per- and polyfluoroalkyl substances (PFAS) to increased risk of several health outcomes, including kidney cancer, testicular cancer, thyroid

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disease, elevated cholesterol. However, the role of PFAS exposure in shaping cardiometabolic risk and subsequent cancer susceptibility among firefighters who face a high burden of occupational exposure to PFAS remains poorly characterized.

Methods: A prospective cohort of firefighters was recruited across eleven counties in California in 2024-2025. Participants provided blood samples and completed several validated questionnaires collecting occupational and demographic characteristics, lifestyle behaviors, and medical history. Blood samples were tested for standard clinical tests (HbA1c, complete metabolic panel, and lipid panel) and concentrations of 24 individual PFAS.

Results: After adjusting for age, we found significant positive associations between years of service as a firefighter and total PFAS (p=0.03). Firefighters with the highest tertile of PFAS had between 46%-66% increased odds of being diagnosed with high cholesterol by a physician depending on the PFAS. For example, the association between branched PFOS and having a diagnosis of high cholesterol was OR=1.51 (95% CI=1.05-2.19) for the highest versus lowest tertile. Furthermore, among firefighters who did not have a prior diagnosis of high cholesterol, levels of some PFAS (including branched PFOS) increased significantly with increasing cholesterol levels (age-adjusted p=0.05). Branched PFOS also increased with increasing levels of creatinine (p<0.001), liver enzymes including ALT (p=0.06), and blood pressure (p<0.001).

Conclusions: Firefighters with high PFAS levels may require screening for cardiometabolic conditions at earlier ages.

Lay Language Abstract: Firefighters experience a higher prevalence of cardiometabolic risk factors and have an additional burden of occupational exposure to per- and polyfluoroalkyl substances (PFAS). Our study examined the relationship between PFAS exposure and cardiometabolic risk in California firefighters.

46 RP-001 INHIBITS PANCREATIC CANCER CELL PROLIFERATION WITH POTENCY COMPARABLE TO GEMCITABINE AND ABRAXANE

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Pancreatic ductal adenocarcinoma (PDAC) has a 13% 5-year relative survival rate for all stages combined, making PDAC hold the highest mortality rate out of all major cancers. To combat this figure, novel compounds that aid patients experiencing PDAC are urgently needed. RP-001 is a novel compound developed for the purpose of targeting and reducing the growth of malignant cells, but its role in PDAC cells remains understudied. I am assessing the dose response curve of RP-001, a cell cycle inhibitor, in PDAC cell lines and comparing that effect to the efficacy and potency of Abraxane and Gemcitabine, chemotherapy drugs, most commonly used as treatment for PDAC patients. For this purpose, I conducted a cell viability assay (MTT test) on MIA Paca-2 and on PANC-1 human pancreatic cancer cells. I plated 10,000 cells per well and treated the cells with RP-001 (0.04, 0.1563, 0.3125, 0.625 μM), Abraxane (0.04, 0.625 μM), Gemcitabine (0.04, 0.625 μM), or a blank nanoemulsion control for 48 and 72 hours. The resulting viability of the treated cells showed that RP-001 decreased the growth of MIA PaCa-2 and PANC-1 human pancreatic cancer cells in a concentration-dependent manner. This same trend was observed with Abraxane and Gemcitabine. At the highest tested concentration of 0.625 μM, RP-001 demonstrated anti-proliferative effects comparable to those of Abraxane and Gemcitabine, with all three agents showing a significant difference from the vehicle control group but no significant difference among treatment groups. In conclusion, RP-001 is a potent new drug with comparable

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potency as Abraxane and Gemcitabine. Additional work is warranted to analyze the cell cycle and apoptotic effects of RP-001, furthering the understanding of RP-001 and forwarding the possibility of RP-001 becoming a suitable treatment for patients with pancreatic cancer.

Lay Language Abstract: Pancreatic Ductal Adenocarcinoma is a deadly disease, warranting studies to expand treatment options. Therefore, I am assessing the efficacy of a novel compound, RP-001, to reduce the growth of human pancreatic cancer cells and comparing this efficacy to that of two chemotherapy drugs commonly used by pancreatic cancer patients, Abraxane and Gemcitabine. Consequently, this compound decreased the growth of human pancreatic cancer cells in a concentration dependent manner and had comparable effects to Abraxane and Gemcitabine.

47 COMPREHENSIVE STATE POLICIES ASSOCIATED WITH THE DELIVERY OF TOBACCO CESSATION SUPPORTS IN U.S. SUBSTANCE USE DISORDER TREATMENT FACILITIES

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Background: Over 70% of adults with a substance use disorder (SUD) use tobacco, and individuals receiving SUD treatment are nearly twice as likely to die of tobacco-related disease (including cancer) than the general population. Integrating tobacco cessation supports into SUD treatment may reduce tobacco-related health disparities and improve treatment outcomes among people with SUD. To address this need for integrated care, 5 states have implemented policies requiring SUD facilities to provide tobacco use screening and cessation treatment (TSCT), 9 states require tobacco-free grounds (TFG) in SUD facilities, and 3 states have implemented both policies.

Objective: This study assessed whether state policies that mandated SUD facilities to offer TSCT and/or provide TFG were associated with facility practice.

Methods: Using cross-sectional data from the 2023 National Substance Use and Mental Health Services Survey and statewide legislative data from the Public Health Law Center, we created a four-category exposure variable to describe state tobacco control policies affecting SUD facilities: states that (1) have no TSCT or TFG policy, (2) have only a TFG policy, (3) have only a TSCT policy, and (4) have both TSCT and TFG policies. We conducted two multivariable logistic regression models using a case duplication approach with cluster-robust standard errors to compare the proportion of facilities that provide TSCT and TFG in these four policy groups.

Results: Among 13,609 facilities, 38.7% offered TSCT and 33.1% reported TFG. States with both TSCT and TFG policies had a higher proportion of facilities offering TSCT (aPR = 1.54, 95% CI = 1.08-2.18) and TFG (aPR = 2.22, 95% CI = 1.60-3.09), compared to states with no policies. States with only TFG policies had a higher proportion of facilities providing TFG compared to states with no policies (aPR = 1.25, 95% CI = 1.10-1.43). There was no association between state policies for only TSCT and facility delivery of TSCT.
Conclusion: Comprehensive policies that require both TSCT and TFG in SUD facilities may increase the delivery of tobacco cessation supports in SUD treatment, which will ultimately improve health outcomes among patients with SUD.

Lay Language Abstract: Patterns of smoking cessation identified in the 2024 Surgeon General's Report on smoking and health indicate a systemic failure to treat tobacco use in substance use disorder (SUD) treatment

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settings. Identifying state policies that are associated with the effective implementation of tobacco cessation supports in SUD treatment is necessary to improve the quality of healthcare systems serving populations disproportionately affected by tobacco-related disease, including cancer. Using cross-sectional data from the 2023 National Substance Use and Mental Health Services Survey and statewide legislative data from the Public Health Law Center, we identified comprehensive state policies that are associated with increased delivery of tobacco cessation supports in U.S. SUD treatment facilities. Our findings can inform efforts to integrate tobacco cessation services and promote smoke-free policies in substance use disorder treatment, which will ultimately improve health outcomes among patients with SUD.

48 INTEGRATING MACHINE LEARNING INTO COLORECTAL CANCER DETECTION

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Colorectal cancer is rising in prevalence and mortality and is the third most commonly occuring and second most fatal form of cancer currently. Cases are expected to rise by 2.2 million, and deaths are predicted to rise by 1.1 million, a 60% increase. Early detection of the disease is critical because over 90% of people treated for early-stage colorectal cancer remain alive five years after diagnosis. Gastroenterologist-interpreted colonoscopies have a 90% accuracy rate in detecting colorectal cancer and can detect about 75% of polyps, but are often not cost-effective, and screening tends to come in later stages. Machine-learning-led research has shown to have a higher average accuracy in predicting certain diseases. It can improve precancerous polyp detection and decrease the need for unnecessary biopsies, as well as improve the detection rate of adenomas to ensure that colonoscopies are more effective. Thus, this project utilizes convolutional neural networks (CNN) to analyze histology images for colorectal cancer. The initial CNN had convolutional layers and was trained on 1024 images classified into eight labels describing the tissue. The CNN was improved through augmented learning that studied flipped and rotated images. Moreover, the study involved adding transfer learning by using the pre-trained CNN and inputting 12 million images for the model to learn from. The original CNN was measured to have a 87.55% accuracy rate but frequently misclassified tumorous tissue as mucosa. The augmented model had a 97.12% accuracy rate but continued to have similar errors in classifying tumors as mucosa. The transfer learning model had a 99.76% accuracy rate and correctly classified most tumor images. This data was transferred to an app-based format where an image of a tissue could be uploaded, and the model would generate probability predictions regarding which tissue was being depicted.

Lay Language Abstract: Colorectal cancer is rising in prevalence and mortality, and is currently the third most common and second most fatal form of cancer. Colonoscopies are the primary way to detect colorectal cancer and have a 90% accuracy rate, but are often cost-ineffective. Machine-learning led research can have a higher accuracy rate in predicting diseases and is more cost-effective, leading to the use of convolutional neural networks, a form of machine learning, to be used in this project to detect colorectal cancer. The CNN has a 99.76% accuracy rate of detecting colorectal cancer when trained on over 12 million images of tissues from the large intestine.

49 ASSESSING REGIONAL DELIVERY OF B7-H3 TARGETING CAR T CELLS VIA PORTAL VENOUS ADMINISTRATION FOR THE TREATMENT OF PANCREATIC CANCER LIVER METASTASES

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease with frequent metastasis to the liver. Novel liver-directed therapies are needed. CAR T therapy has shown great clinical success in hematological malignancies but has shown limited efficacy in the setting of solid tumors, including advanced PDAC. Primary challenges to CAR T therapy for solids 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 through the 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 106 luciferase-tagged PANC-1 cells into NSG mice via hemi-spleen method. Tumor burden was assessed by bioluminescent imaging. After 14 days, B7-H3 CAR T or untransduced (UnT) T cells (107 cells/kg dose) were injected into the portal vein and survival and tumor burden were assessed. Additionally, PDAC liver mets were treated 14 days after tumor implantation with 106 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 portal venously administered matched untransduced T cells. B7-H3 CAR T cells administered via portal vein showed increased liver engraftment five days after administration compared to CAR T cells administered intravenously (3.9x105 vs 2.6x104 CAR T cells per mg liver tissue, P<0.001). CD8 CAR T cells administered via portal vein also demonstrated higher expression of liver tissue residency markers including CD49a (36.5% vs 11.7%, P<0.0001), CXCR6 (13.0% vs 5.9%, P=0.0001), and CD103 (17.1% vs 10.5%, P<0.0001).

Conclusion: 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 regional delivery of B7-H3 CAR T therapy via the portal vein to treat PDAC liver metastases and support early phase clinical studies of portal venous cellular therapy.

Lay Language Abstract: Pancreatic cancer is a deadly disease that frequently spreads to the liver. Developing therapies that specifically target the liver are needed to improve outcomes for patients with pancreatic cancer. Immunotherapies such as chimeric antigen receptor (CAR) T cells therapy have shown great success for patients with certain blood cancers, but have yet to show success in solid tumors including metastatic pancreas cancer largely due to challenges with trafficking and engraftment within the tumor. The goal of this project is to optimize CAR T therapy specifically for the liver by delivering CAR T therapy directly to the liver through the portal vein to treat pancreatic cancer liver metastases.

50 A NOVEL APPROACH TO TRIPLE-NEGATIVE BREAST CANCER: PIP5K1 INHIBITION AS A STRATEGY TO SUPPRESS PI3K/AKT AND PLC PATHWAYS

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Triple-negative breast cancer (TNBC) is one of the most difficult breast cancer subtypes to treat and currently lacks targeted therapies or a definitive cure. While chemotherapies and immunotherapies have been developed to combat TNBC, their efficacy is limited. One of the key tumor-promoting pathways in TNBC is the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling cascade. Although some AKT-targeting therapies exist, they are typically used in combination regimens or as second-line treatments. A critical upstream enzyme in this pathway is phosphatidylinositol 4- phosphate 5-kinase 1 (PIP5K1), a lipid kinase that generates phosphatidylinositol 4,5-bisphosphate (PIP2), the substrate for both PI3K and phospholipase C (PLC). Through this dual role, PIP5K1 regulates both PI3K/AKT and PLC signaling, the latter of which produces key secondary messengers, inositol triphosphate (IP3) and diacylglycerol (DAG). Notably, there are currently no FDA-approved inhibitors of PIP5K1, representing an untapped therapeutic opportunity. We have developed a novel small-molecule inhibitor (SMI 299) targeting PIP5K1, which shows threefold greater toxicity and greater inhibition of phosphorylated AKT compared to two existing preclinical PIP5K1 inhibitors. Moving forward, we aim to: (1) assess cellular toxicity and pathway inhibition, (2) evaluate intrinsic cell death and potential off-target effects following our SMI treatment, and (3) investigate the toxicity and therapeutic efficacy of our SMI 299 in vivo. We hypothesize that PIP5K1 inhibition via SMI 299 will suppress tumor growth and progression by simultaneously disrupting the PI3K/AKT and PLC pathways in both in vitro and in vivo TNBC models. This novel therapeutic strategy may address a critical treatment gap in TNBC by offering enhanced specificity and efficacy.

Lay Language Abstract: Triple-negative breast cancer (TNBC) is one of the hardest types of breast cancer to treat because it lacks targeted treatments. Our research focuses on targeting a key lipid kinase that promotes cancer cell growth and survival. We developed a new experimental treatment that blocks this lipid kinase; early results indicate it may improve treatment compared to similar treatments currently being studied. Next, we will test whether this treatment can safely slow or stop tumor growth, potentially leading to a new treatment option for TNBC patients.

51 INVESTIGATING IF THE MODULATION OF THE GUT MICROBIOME BY A NOVEL DRUG ENHANCES TUMOR IMMUNE INFILTRATION IN PANCREATIC CANCER

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Anti-PD-1 is a type of immunotherapy that helps the immune system recognize and eliminate cancer cells by targeting the programmed cell death-1 receptor of cytotoxic CD8+ T cells. Anti-PD-1 has shown therapeutic efficacy in various malignancies. However, its efficacy in pancreatic ductal adenocarcinoma (PDAC) remains poorly characterized, highlighting the need to identify factors that enhance its therapeutic response. The gut microbiome has emerged as a critical modulator of immunotherapy efficacy. Thus, this study aims to determine whether modulating the gut microbiome with RP-001, a novel derivative of the chemotherapeutic paclitaxel, enhances immune infiltration in KPC mice, a genetically engineered mouse model of PDAC. Briefly, KPC mice (n=5-8) were treated with a broad-spectrum antibiotic cocktail via oral gavage before and throughout treatment to deplete gut microbiota. Anti-PD-1 was administered intraperitoneally twice weekly (200 µg), and RP-001 was delivered intravenously once weekly (10 mg/kg) for three weeks. Preliminary results show that depletion of the gut microbiome with antibiotics reverses the enhanced tumor infiltration of CD8+ T cells induced by RP-001

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and anti-PD-1 therapy. These findings will clarify the role of the gut microbiome in shaping immunotherapy response and inform future strategies to improve efficacy in patients with PDAC.

Lay Language Abstract: Pancreatic cancer is one of the most difficult cancers to treat, primarily due to treatment-resistant cancer cells. Immunotherapy drugs like anti-PD-1 work by boosting the immune system's ability to find and destroy cancer, but they have shown limited success in pancreatic cancer patients. Our research investigates whether altering the gut microbiome, the collection of microorganisms living in our digestive system, can improve how well immunotherapy works in pancreatic cancer. Using a mouse model, we found that removing the gut microbiome with antibiotics reversed the increase in immune cells entering the tumor. These findings suggest that the gut microbiome plays an important role in enhancing immunotherapy, and could inform future strategies to improve efficacy in patients.

52 ROLE OF LIVER-DIRECTED RADIATION THERAPY IN COMBINATION WITH B7-H3 CAR T THERAPY TO TREAT PDAC LIVER METASTASES

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Introduction: Chimeric antigen receptor (CAR) T cells have proven unsuccessful in most advanced solid tumors, including pancreatic ductal adenocarcinoma (PDAC), a lethal disease characterized by frequent liver metastases. Radiation therapy (RT) has been shown to improve CAR T efficacy in certain pre-clinical models and liver-directed RT may improve CAR T therapy through altering tumor antigen expression and inflammatory responses. We investigated the impact of liver-directed RT to augment B7-H3 CAR T cell function.

Methods: PANC-1 cells were treated with 0-8 Gy RT in vitro and analyzed by flow cytometry or bulk RNA-sequencing 48 hours post-RT. mCherry-labeled PANC-1 cells were treated with 0 Gy or 4 Gy RT. 48 hours later, B7-H3 CAR T cells or untransduced T cells were added at 1:5, 1:1, and 2:1 effector-to-target ratios and PANC-1 cell killing was assessed by fluorescence using IncuCyte live-imaging over 72 hours. Xenogeneic PDAC liver metastases were generated by injecting 106 luciferase-tagged PANC-1 cells into NSG mice via hemi-spleen method. Five weeks later, mice were treated with 0 Gy or 4 Gy liver-directed RT and liver tumors were analyzed 48 hours later by flow cytometry.

Results: RNA sequencing of RT-treated PANC-1 cells demonstrated upregulation of several pathways including radiation-response score, adhesion molecules including ICAM-1, interferon gamma signaling, and immune cell recruiting chemokines, suggesting a proinflammatory response. PANC-1 cells treated with 0-8 Gy RT in vitro demonstrate increased CAR target antigen B7-H3 by median fluorescent intensity (MFI) as well as adhesion molecule ICAM-1 by percent expression and MFI. B7-H3 CAR T cells in combination with RT showed increased in vitro killing of PANC-1 cells compared to CAR T alone at multiple effector-to-target ratios. NSG mouse liver metastases treated with 4 Gy of RT demonstrated increased B7-H3 by percent expression and MFI compared to untreated liver metastases.

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Conclusions: RT treatment of target cells results in greater expression of B7-H3 and proinflammatory markers, enhancing CAR T cell killing in vitro. Increased B7-H3 expression is also seen in vivo after liver-directed RT treatment in metastasis-bearing mice. Liver-directed RT may be a strategy to improve targeting PDAC liver metastases with CAR T cellular therapy.

Lay Language Abstract: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive and deadly cancer that often has liver metastases and a low survival rate. While chimeric antigen receptor (CAR) T immunotherapies have been successful in treating blood cancers, they have not been successful in treating PDAC and other solid tumors. Our goal was to assess if radiation helps with the efficacy of CAR T treatment in PDAC liver metastases.

53 3D-BIOPRINTED TUMOR MODEL CAN BETTER MODEL ANDROGEN SIGNALING DYNAMICS AND DRUG SENSITIVITIES IN TRAMP-DERIVED CELL LINE

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Transgenic adenocarcinoma of the mouse prostate (TRAMP) models are widely used to study prostate cancer biology and therapeutic response. Tumors arising in these mice can be harvested to generate TRAMP-derived cell lines that serve as experimental platforms for mechanistic and therapeutic investigations. However, conventional two-dimensional (2D) culture systems fail to recapitulate key features of the tumor microenvironment that influence androgen signaling and drug response. To address this limitation, we evaluated the behavior of TRAMP-derived prostate tumor cells in a three-dimensional (3D) bioprinted tumor model designed to better preserve tumor architecture and signaling context.

Two aggressive TRAMP tumors were used to generate cell lines that were expanded and incorporated into a collagen-based 3D bioprinted system. Immunofluorescence analysis confirmed retention of key prostate cancer markers, including prostate-specific membrane antigen (PSMA) and NKX3.1. Functional studies revealed a strong androgen-dependent phenotype. In particular, the TRAMP–derived 255 cell line failed to establish or maintain growth in 3D culture without dihydrotestosterone (DHT), indicating persistent androgen dependence. Importantly, this androgen-supported growth was selectively inhibited by the androgen receptor antagonist darolutamide in the 3D system. Notably, this darolutamide sensitivity was not observed in conventional 2D culture, highlighting a context-dependent therapeutic response revealed only in the 3D model.

Together, these findings demonstrate that 3D bioprinted tumor models can uncover biologically relevant androgen signaling dynamics and drug sensitivities that are not evident in standard 2D systems. These models may therefore provide a more physiologically relevant platform for studying prostate cancer biology and evaluating therapeutic response.

Lay Language Abstract: Transgenic adenocarcinoma of the mouse prostate (TRAMP) models and TRAMP-derived cell lines are important tools in the study of prostate cancer therapeutics. However, traditional 2D models often fail to model components of the tumor microenvironment that are necessary to adequately the androgen signaling and drug mechanisms. To overcome this limitation, we are investigating the use of a 3D bioprinted system using two TRAMP-derived cell lines that show expression of key prostate-specific markers. These studies have shown that in 3D culture, these cell lines need the presence of androgens for survival

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while also showing sensitivity to androgen receptor targeting drugs, a characteristic that is not observed in 2D cultures. These findings indicate 3D models can provide a more physiologically relevant platform for the study of prostate cancer biology.

54 HIGH MOBILITY GROUP A1 (HMGA1) PROMOTES HIGH GRADE SOFT TISSUE SARCOMA PULMONARY METASTASIS

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Metastasis is the leading cause of death in patients with soft tissue sarcoma (STS), yet the molecular mechanisms driving metastasis remain poorly understood. Sarcomas are a group of rare and heterogenous tumors of mesenchymal origin. Despite aggressive multimodal treatment patients with metastatic disease have a poor prognosis with 30% survival at 3 years. To identify drivers of STS metastasis we utilized a spontaneous metastasis model in which tumors implanted into the mouse calf metastasize to the lung, mimicking the pattern of disease in humans. Differential expression analysis comparing genes upregulated in metastatic lesions versus the primary tumor identified HMGA1, an epigenetic regulator, as significantly enriched in metastatic lesions. Consistent with this observation, analysis of sarcoma samples from the cancer genome atlas (TCGA) revealed that elevated HMGA1 expression correlates with poor overall survival.

To evaluate HMGA1 as a driver of lung metastasis, we depleted HMGA1 in a metastatic sarcoma cell subline and injected control or HMGA1KO cells into the calf of mice. Metastatic progression was monitored using bioluminescence imaging. Control mice developed lung metastases within two weeks, as indicated by total flux and reached endpoint by six weeks. In contrast, HMGA1KO mice showed no detectable lung metastases during this period. Because HMGA1KO tumors formed more slowly, we extended this study to 13 weeks, at which point primary tumors reached a weight comparable to controls but exhibited minimal lung metastasis. Histological analysis of lung sections further confirmed these findings, revealing significantly fewer and smaller lung lesions in HMGA1KO mice.

In vitro studies further revealed that HMGA1 depletion reduces metastatic cell behaviors including proliferation, migration and invasion suggesting a critical role during sarcoma metastasis. Further, transcriptomic analysis identified WNT7B, a critical regulator of beta-catenin signaling, as significantly downregulated following HMGA1 loss indicating this may be a key target in HMGA1-associated metastasis. Notably, patients with high WNT7B expression exhibited reduced five-year survival, validating the importance of investigating this factor. Current studies in the lab are investigating the HMGA1-WNT7B axis.

These findings implicate an HMGA1-driven program that promotes pulmonary metastasis and highlights the HMGA1-WNT7B axis as a potential therapeutic vulnerability in metastatic STS which warrants further investigation.

Lay Language Abstract: Soft tissue sarcomas are rare cancers that frequently spread to the lungs, and patients with metastatic disease often have poor survival outcomes. Our lab aims to understand the biological mechanisms that enable sarcoma cells to metastasize. We identified HMGA1 as highly expressed in metastatic tumors and demonstrated that its loss can prevent metastatic spread. These findings may help guide the development of new strategies for treating metastatic sarcoma.

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55 MALIGNANT HEMANGIOPERICYTOMA: A NATIONAL CANCER DATABASE STUDY OF DEMOGRAPHIC AND SOCIOECONOMIC FACTORS

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Background: Malignant hemangiopericytoma (HPC) is a rare solitary fibrous tumor arising from pericytes surrounding small blood vessels. In the United States, the estimated annual incidence of central nervous system (CNS) HPC is 0.6 cases per million. Prior case series suggest poor prognosis, with high rates of recurrence and metastasis. Diagnosis is challenging due to nonspecific imaging findings, and large-scale epidemiologic data remain limited. This study used the National Cancer Database (NCDB) to characterize demographic, socioeconomic, and clinical features of malignant HPC.

Methods: A retrospective cohort study was conducted (N = 1,648) using NCDB data from 2004-2020. Demographic, socioeconomic, tumor, treatment, and facility-level variables were analyzed using descriptive statistics. Incidence trends were evaluated using regression analysis.

Results: Incidence remained stable over the study period ($R^2 = 0.04$). Mean age at diagnosis was 52.7 years (SD = 16.2), with near-equal sex distribution (51.5% female). Patients were predominantly White (83.3%), non-Hispanic (87.5%), privately insured (56.4%), and metropolitan residents (53.2%). Most had low comorbidity burden (78.6% Charlson–Deyo score 0). The cerebral meninges was the most common primary site (24.8%). Radiation therapy was the most common primary treatment (54.1%), often delivered at academic or comprehensive cancer programs. Overall survival was 80.2% at five years and 58.9% at ten years.

Conclusion: This first NCDB analysis of malignant HPC highlights stable incidence, near-equal sex distribution, and concentration of care in academic settings. Further research is needed to understand how demographic and socioeconomic factors influence diagnosis, treatment decisions, and long-term outcomes for this rare malignancy.

Lay Language Abstract: Malignant hemangiopericytoma (HPC) is a rare type of tumor that develops from cells surrounding small blood vessels. Because it is uncommon and difficult to identify through imaging alone, it is often diagnosed only after a tissue biopsy. In this study, researchers analyzed a large national cancer database to better understand who is most affected by this tumor and how patients are treated. The findings show patterns in demographics, treatment settings, and survival outcomes, which can help guide future research and improve care for people diagnosed with this rare cancer.

56 MULTIFUNCTIONAL AND SCALABLE NANOPARTICLES FOR BIMODAL IMAGE-GUIDED PHOTOTHERAPY IN BLADDER CANCER TREATMENT

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Rational design of multifunctional nanoplatforms capable of combining therapeutic effects with real-time monitoring of drug distribution and tumor status is emerging as a promising approach in cancer nanomedicine. Here, we introduce pyropheophorbide a–bisaminoquinoline conjugate lipid nanoparticles (PPBC LNPs) as a bimodal system for image-guided phototherapy in bladder cancer treatment. PPBC LNPs not only demonstrate both powerful photodynamic and photothermal effects upon light activation, but also exhibit potent autophagy blockage, effectively inducing bladder cancer cell death. Furthermore, PPBC LNPs possess remarkable photoacoustic (PA) and fluorescence (FL) imaging capabilities, enabling imaging with high-resolution, deep tissue penetration and high sensitivity for tracking drug biodistribution and phototherapy efficacy. Specifically, PA imaging confirms the efficient accumulation of PPBC LNPs within tumor and predicts therapeutic outcomes of photodynamic therapy, while FL imaging confirms their prolonged retention at the tumor site for up to 6 days. PPBC LNPs significantly suppress bladder tumor growth, with several tumors completely ablated following just two doses of the nanoparticles and laser treatment. Additionally, PPBC LNPs were formulated with lipid-based excipients and assembled using microfluidic technology to enhance biocompatibility, stability, and scalability, showing potential for clinical translation. This versatile nanoparticle represents a promising candidate for further development in bladder cancer therapy.

Lay Language Abstract: Treating bladder cancer is challenging because deep tumors are difficult to map precisely, and cancer cells often activate survival mechanisms to resist therapy. To solve this, we developed easily mass-produced "smart" nanoparticles that both visualize and destroy bladder cancer. These tiny particles act as bright beacons, lighting up tumors on medical scans for accurate tracking. Once activated by a targeted laser, the particles generate intense heat and highly reactive oxygen to destroy the tumor. Crucially, they also block the cells' ability to repair, preventing them from surviving the damage. This multi-targeted approach overcomes therapy resistance, offering a highly precise bladder cancer treatment.

57 MOLECULAR CHARACTERIZATION OF GASTRIC CANCER PATIENT-DERIVED MODELS REVEALS TARGETABLE CANCER DRIVER PATHWAYS

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Gastric cancer (GC) is a leading cause of cancer-related deaths worldwide, with significant racial and ethnic disparities in the United States. Latinos experience a higher incidence compared to non-Latino whites. Current molecular characterization efforts, such as The Cancer Genome Atlas (TCGA), lack Latino patient data, with only 0.4% of its samples representing Latinos and American Indians/Alaskan Natives. To address this gap, the University of California Minority Patient-Derived Xenograft (PDX) Development and Trial Center (UCaMP) and the University of California and the University of Texas Southwestern (UCaTS) Diversity Patient-Derived Xenograft (PDX) Development and Trial Center are establishing GC models that reflect the populations most affected and to find treatments for these patients. So far, we have established 35 preclinical models with 35% of samples from patients with a Latino background. Our goal is to molecularly characterize PDOs to identify targetable vulnerabilities. With digital droplet PCR (ddPCR), cancer driver genes involved in CDK4/6,

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PI3K/AKT, and RAS/MEK signaling pathways were interrogated. DNA and RNA were harvested from our PDOs and 4 commercially available GC cell lines to investigate copy number variations (CNVs), gene expression, and mutations. Optimization of the multiplex assays improved cluster separation and corrected target quantification. Models that express cancer driver genes are subjected to the investigation of select inhibitors that target that pathway. As a proof of concept, we confirmed HER2 overexpression in the NCI-N87 cell line and found sensitivity to HER2 inhibitors trastuzumab-deruxtecan and trastuzumab-emtansine. Our efforts in understanding the genetic landscape of our racially and ethnically diverse GC models will aid in improving patient care.

Lay Language Abstract: In the U.S., certain racial and ethnic groups, like Latinos, are more at risk for developing stomach cancer. Most research has focused on non-Latino populations, leaving important gaps in understanding the disease. Our work creates patient-derived gastric cancer models from diverse populations to study the genetic drivers of the disease and test treatments that could better help these communities.

58 REAL-WORLD CARDIOVASCULAR EVALUATION AND CLINICAL IMPLICATIONS IN PATIENTS WITH ADVANCED LUNG CANCER TREATED WITH IMMUNE CHECKPOINT INHIBITORS

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Background: Cardiovascular immune-related adverse events (CV irAEs) are increasingly recognized with the expanding use of immune checkpoint inhibitors (ICIs). Current NCCN Guidelines (v1.2025) for Immunotherapy-Related Adverse Events recommend baseline cardiovascular assessment, including electrocardiogram (ECG), high-sensitivity troponin, and N-terminal pro–B-type natriuretic peptide (NT-proBNP), with selective longitudinal monitoring in patients with abnormal baseline findings or new cardiopulmonary symptoms. However, these recommendations are largely based on expert consensus. We performed a real-world analysis of cardiovascular testing patterns and clinical outcomes in patients with advanced lung cancer receiving ICIs.

Methods: We retrospectively evaluated utilization of ECG, transthoracic echocardiography (TTE), troponin, and NT-proBNP in 399 lung cancer patients treated with ICIs between October 2014 and December 2023. Abnormal cardiovascular findings were defined as left ventricular systolic dysfunction (LVSD; LVEF <50%), marked QTc prolongation (≥500 ms), or elevated cardiac biomarkers indicative of myocardial injury (troponin T/I) or myocardial stress (NT-proBNP). Associations between cardiovascular abnormalities and median overall survival (mOS), measured from ICI initiation to death, were assessed using one-way ANOVA and Kruskal–Wallis tests, with multivariable modeling.

Results: The median age was 68 years (range 22–94), and 50.4% of patients were female. Most patients had non-small cell lung cancer (76.4%), and over 90% received ICI monotherapy. Substantial heterogeneity was observed in the frequency and abnormality rates of cardiovascular testing. Patients with LVSD experienced significantly worse mOS compared with those with preserved LVEF (3.9 vs. 6.8 months, p=0.019). Among 49 patients with LVSD, most demonstrated partial or complete recovery with multidisciplinary cardio-oncology management, including four cases (8.2%) consistent with stress-induced (Takotsubo) cardiomyopathy. In

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multivariable analyses, combined ECG abnormalities and elevated NT-proBNP showed the strongest association with overall survival (p=0.009), followed by ECG with troponin elevation (p=0.03) or NT-proBNP alone (p=0.01). Long-term surveillance for chronic cardiovascular sequelae is ongoing.

Conclusions: Prospective validation of guideline-directed cardiovascular surveillance strategies incorporating ECG, echocardiography, and cardiac biomarkers is needed to enable risk stratification, early detection, and mitigation of CV irAEs during and after ICI therapy.

Lay Language Abstract: This study focused on heart health in patients with immune checkpoint inhibitors (ICIs) treated for advanced lung cancer. While these drugs can be effective against cancer, they can sometimes cause heart-related side effects, but current screening recommendations are mostly based on expert opinion rather than real-world data. By reviewing nearly 400 patients, the researchers found wide variation in how often heart tests were performed and discovered that certain heart problems—especially weakened heart function or abnormal heart tests—were linked to shorter survival. Encouragingly, many patients with heart dysfunction improved with specialized cardio-oncology care. The findings highlight the need for clearer, evidence-based heart monitoring strategies to detect and manage cardiac side effects early during cancer treatment.

59 EMERGENCY DEPARTMENT ENCOUNTERS AMONG UC DAVIS HEALTH ACTIVE CANCER REGISTRY PATIENTS BY CANCER TYPE AND REASON FOR ENCOUNTER

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Background: Individuals with cancer represent a vulnerable patient population who often receive acute care in the Emergency Department (ED). Although ED care can provide rapid symptom evaluation, it also poses the challenges of high medical costs, risk of unnecessary diagnostics and/or treatments, and fragmented care. To better understand the ED utilization patterns among patients with cancer, we evaluated ED encounters stratified by cancer type and reason for encounter.

Methods: We identified patients in the UC Davis Health Active Cancer Registry with at least one ED encounter between January 1, 2025, and December 31, 2025. We used ICD 10-CM codes to categorize cancer diagnoses by type, excluding secondary and nonmelanoma skin cancers. We quantified the 10 most frequent cancer types among patients with ED encounters. Among the ED encounters at UC Davis Health with a known primary ED diagnosis, we observed the most common reason for ED encounters by cancer type.

Results: There were 4,621 ED encounters made by 2,627 patients. Most patients (63.0%) had a single encounter, while 29.1% had 2–3 encounters, 5.1% had 4–6, and 2.7% had 7 or more. The 10 most frequent primary cancer types were prostate (9.4%), breast (8.9%), acute and chronic leukemia (8.4%), non-Hodgkin lymphoma (7.9%), lung (7.4%), colorectal (5.8%), brain (3.8%), myeloma (3.2%), kidney (3.1%), and pancreatic (2.9%). Of known ED encounter reasons, the most frequent by cancer type were gastrointestinal (e.g., abdominal pain, nausea, constipation) for breast, non-Hodgkin lymphoma, colorectal, kidney, and pancreatic cancers; urogenital (e.g., hematuria, kidney or bladder inflammation) for prostate; hematologic (e.g., anemia) for leukemia; respiratory (e.g., shortness of breath, chronic obstructive pulmonary disease (COPD) exacerbation) for lung; neurologic (e.g., headache, dizziness) for brain; and musculoskeletal/pain-related reasons for myeloma.

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Conclusion: Understanding ED utilization by cancer type and reason for ED visit can inform population health interventions to increase outpatient and safe home-based care and subsequently decrease preventable ED visits. Based on our findings, efforts to relieve neurologic symptoms including headaches and dizziness, gastrointestinal symptoms including abdominal pain, nausea, and constipation, management of COPD symptoms to avoid exacerbation, and ongoing chronic pain management may reduce ED encounters among cancer patients.

Lay Language Abstract: Individuals with cancer represent a vulnerable patient population who often receive acute care in the Emergency Department (ED). While ED care can provide rapid symptom evaluation, it also poses the challenges of high medical costs, risk of unnecessary diagnostics and/or treatments, and fragmented care. To better understand the ED utilization patterns among patients with cancer, we evaluated ED encounters stratified by cancer type and reason for encounter. Based on our findings, efforts to relieve neurologic symptoms including headaches and dizziness, gastrointestinal symptoms including abdominal pain, nausea, and constipation, management of COPD symptoms to avoid exacerbation, and ongoing chronic pain management may reduce ED encounters among cancer patients.

60 METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA-DERIVED EXTRACELLULAR VESICLES FACILITATE PRE-METASTATIC NICHE CONDITIONING IN THE LUNGS

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Head and neck squamous cell carcinoma (HNSCC) is associated with high morbidity and mortality. While current treatments are effective for early-stage disease, outcomes for recurrent or metastatic HNSCC remain poor, and existing biomarkers fail to predict or prevent metastasis. Additionally, the lack of spontaneous lung SCC metastasis models in an immunocompetent background has hindered mechanistic studies. Tumor-derived extracellular vesicles (EVs) have been implicated in pre-metastatic niche formation in other cancers. Here, we use immunocompetent models to define the stage of metastasis at which SCC-derived EVs promote metastasis and to identify their cellular and molecular targets.

Lay Language Abstract: Head and neck cancer is associated with high mortality, often due to metastasis. Current standard-of-care treatments can effectively treat early-stage disease, but outcomes remain poor for recurrent or metastatic cases, and there are few reliable ways to predict or prevent the cancer from spreading. Our research studies nanoparticles released by cancer cells, called extracellular vesicles, which may help prepare distant organs for tumor growth. Using mouse models with intact immune systems, we investigate how these particles promote metastasis and influence cells in distant organs to create a tumor-permissive environment.

61 DIETARY OMEGA-3 POLYUNSATURATED FATTY ACIDS ATTENUATE OBESITY AND ASSOCIATED DISORDER IN MICE: POTENTIAL IMPORTANCE OF CYTOCHROME P450-DERIVED OMEGA-3 FATTY ACID EPOXIDES

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Objectives: Human and preclinical studies have shown that a high intake of omega-3 polyunsaturated fatty acids (PUFAs) is associated with a reduced risk of obesity and related disorders. However, the underlying mechanism remain poorly understood. The objective of this study was to investigate the effects and mechanisms of dietary omega-3 PUFAs on obesity.

Methods: We treated C57BL/6 mice with a low-fat diet, a high-fat diet, or omega-3 PUFA-enriched high-fat diets, then the development of obesity, adipose inflammation and dysfunction, and other metabolic disorders were studied. In addition, we used LC-MS/MS-based lipidomics, which can analyze >100 lipid metabolites, to study how omega-3 PUFA intake modulates obesity-associated lipid metabolism.

Results: Dietary administration of omega-3 PUFA reduced obesity development in a dose-dependent manner, illustrating the anti-obese effects of omega-3 PUFAs. LC-MS/MS lipidomics showed that omega-3 intake significantly altered the profiles of lipid metabolites in tissues, with cytochrome P450-derived omega-3 fatty acid epoxides showing the most pronounced increase.

Conclusions: Our studies support the anti-obese effects of dietary omega-3 PUFAs. Furthermore, the lipidomics analysis suggests that omega-3 epoxides may play a key role in the health benefits of omega-3 PUFAs.

Funding Sources: This research is supported by a new faculty start-up grant from the University of California Davis (to G.Z.).

Lay Language Abstract: Eating more omega-3 fats—found in foods like fish and some plant oils—can help protect against weight gain and related health problems, but how they work has not been fully clear. In this study, we found that diets rich in omega-3 fats reduced obesity and inflammation in mice, with greater benefits seen at higher intakes. Using advanced techniques to measure many fat-derived molecules in the body, we discovered that omega-3 intake strongly increased a specific group of beneficial molecules called omega-3 epoxides. These findings suggest that omega-3 fats may help prevent obesity by changing how fats are processed in the body, and that omega-3 epoxides could be key drivers of these health benefits.

62 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 aberrantly reactivated in advanced prostate cancer. ASCL1 drives neuroendocrine differentiation by activating neuronal genes and cooperating with N-Myc and EZH2 to promote androgen receptor (AR) independence and therapy resistance. ASCL2, regulated by Wnt/β-catenin signaling, maintains stem-like programs and facilitates epithelial-to-neuroendocrine transition under androgen deprivation. Both factors promote lineage plasticity leading to castration-resistant and neuroendocrine prostate cancer (NEPC). This study examines their distinct gene expression patterns to elucidate how ASCL1 and ASCL2 contribute to lineage transitions and identify potential targets to block transdifferentiation and therapeutic resistance.

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Methods: Spatial transcriptomic profiling was performed on a Gleason 10 prostate cancer specimen using the 10x Genomics Visium platform. Regions with ASCL1-high, ASCL2-high, or ASCL1/ASCL2-low expression were analyzed for differential gene expression using Loupe Browser, heatmaps, volcano and violin plots, and pathway enrichment via Gene Set Enrichment Assay (GSEA). A patient derived (PDX) model derived from the same patient was subjected to castration, and intact (n=4) and relapsed (n=6) tumors underwent bulk RNA-seq and GSEA. A spontaneously immortalized prostate cancer cell line, UCDCaP, was derived from the same patient, and its castration-resistant derivative, UCDCaP-CR, was established through serial castration-relapse cycles and mouse passages. Key genes were validated by qRT-PCR and Western blotting.

Results: ASCL1 and ASCL2 were expressed in a mutually exclusive manner in prostate cancer patient tissues. Compared with ASCL2-high regions, ASCL1-high areas showed higher expression of WNT5A, FOLH1 (PSMA), KRT15, INSM1, HES6, PEG10, and PROX1, but lower levels of AR, AKR1C3, MAOA, and MET. GSEA indicated enrichment of E2F, Myc, DNA repair, translation, and neural lineage pathways in ASCL1-high regions, while interferon signaling, androgen response, extracellular matrix, and epithelial-mesenchymal transition (EMT) pathways were enriched in ASCL2-high regions. Castration-relapsed PDX tumors exhibited increased AR, AKR1C3, CA9, ASCL1, and ASCL2, with reduced FOXA1, FOXJ1, DUSP1, and ALDH1A3. Parallel analyses in UCDCaP-CR cells showed upregulated ASCL2 and neuroendocrine markers, and downregulated ASCL1, PTEN, AR response, and P53 pathways.

Conclusions: ASCL1 and ASCL2 define distinct molecular states in prostate cancer. ASCL1 is linked to neural lineage and proliferative pathways, whereas ASCL2 is associated with androgen response and EMT programs. Their mutual exclusivity suggests divergent mechanisms of lineage plasticity. The transition toward ASCL2 dominance in castration-relapsed models, accompanied by neuroendocrine marker upregulation and loss of AR and P53 signaling, highlights their dynamic interplay in driving therapy resistance and neuroendocrine differentiation.

Lay Language Abstract: Spatial transcriptomics of advanced prostate cancer reveals that ASCL1 and ASCL2 are expressed in a mutually exclusive manner, defining two distinct molecular states. ASCL1-high regions are associated with neural lineage pathways, E2F/Myc activity, and high expression of markers like WNT5A and INSM1, while ASCL2-high regions are enriched for androgen response, EMT, and interferon signaling. In castration-relapsed patient-derived models, a dynamic shift toward an ASCL2-dominant state occurs, accompanied by the upregulation of neuroendocrine markers and the loss of AR and P53 signaling. These findings suggest that ASCL1 and ASCL2 drive divergent mechanisms of lineage plasticity and therapy resistance, highlighting potential targets to block neuroendocrine transdifferentiation in castration-resistant prostate cancer.

63 UNDERSTANDING DELAYS IN DEFINITIVE TREATMENT FOR RECTAL CANCER

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Introduction: In a retrospective review, we found that female sex and distance greater than 60 miles were associated with significant delays in definitive treatment for rectal cancer, which affects patient outcomes. This study seeks to further understand contributory factors to delays in care of these rectal cancer patients.

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Methods: Semi-structured interviews were conducted with 24 adult patients with a diagnosis of rectal cancer at a tertiary cancer institution. Interviews were conducted via telephone call, audio-recorded and digitally transcribed. Transcriptions were coded and thematic analysis was conducted to understand delays in rectal cancer care.

Results: Through qualitative analysis, four main themes emerged (figure 1): (1) patient perception of disease, (2) provider communication, (3) social determinants of health, and (4) fragmentation of care. Patients highlighted a lack of literacy regarding rectal cancer and its signs and symptoms, leading to delays in initial diagnosis. Participants were satisfied with care even when definitive treatment was delayed. However, they recognized transitioning care to a facility more convenient in location, as essential to facilitating care and patient satisfaction.

Conclusions: Increased awareness and literacy for rectal cancer and its presentation in the general population is vital to early diagnosis and treatment. Connection with providers and transitioning care to a more convenient method, such as telehealth or facilities closer to patient homes, encourage decreased fragmentation and delays in care.

Lay Language Abstract: Our study explores why some patients with rectal cancer experience delays in receiving treatment. Through interviews with patients, we found that limited awareness of rectal cancer symptoms, challenges in communication with healthcare providers, social factors such as travel distance, and fragmented care between medical facilities all contributed to delays. Many patients lived far from specialized cancer centers, making it harder to access timely care. Improving public awareness of symptoms and expanding convenient care options—such as telehealth or treatment closer to patients' homes—may help patients receive earlier diagnosis and treatment.

64 PREDICTIVE Y-90 DOSIMETRY FOR LIVER CANCER USING DEEP GENERATIVE MODELS

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Yttrium-90 (Y-90) microsphere radioembolization, a targeted treatment injected into the liver bloodstream, has been shown to improve outcomes of advanced liver cancer. Treatment planning currently involves a qualitative assessment of (CT) angiography. The use of computational fluid dynamics simulations of blood flow and microsphere transport in arterial branches may provide more precise microsphere distribution predictions. This process is resource-intensive and remains incompatible with the clinical workflow. There is a need to develop more efficient treatment planning methods for Y-90, as the quality of the treatment greatly 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.

A 3-dimensional conditional Generative Adversarial Network (cGAN) designed to generate realistic Y-90 distributions resembling post-treatment PET images. The generator is composed of a U-Net style encoder-decoder. Contrast-enhanced computed tomography (CECT) images in the late arterial phase provide information about vascular supply in the liver. Pre-treatment CECT images from 30 subjects were used to create the training dataset of 4008 paired images. Ground-truth Y-90 PET images were acquired on the GE 690 and uEXPLORER scanners. The network was trained for 10000 epochs on a GPU-based workstation. The

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generated distributions were initially visually compared to activity distributions derived from true Y-90 PET images followed by a quantitative assessment via mean absolute error, structural similarity index measure (SSIM), and learned perceptual image patch similarly (LPIPS).
The cGAN was able to generate realistic output with a close match in spatial distribution between the generated images and the reference distributions. For Y-90 distributions generated from a representative subject's CECT, mean absolute error was 0.001, SSIM reached 0.970, and LPIPS reached 0.030 relative to the reference images in the testing dataset.

Lay Language Abstract: This study demonstrates the feasibility of using generative adversarial networks to predict Y-90 activity based on late arterial phase CECT imaging. Additional work will include fine-tuning of network hyperparameters in order to provide a more generalizable output and an ability to iterate the injection point for treatment planning.

Liver cancer treatment planning can be improved via the use of artificial intelligence. It is important to quickly predict the drug distribution before treatment. This can inform the physicians on the optimal dosage and injection point.

65 RAPID PRE-ONSET INCREASES IN NEUTROPHIL-TO-LYMPHOCYTE RATIO IDENTIFY MILD AND SEVERE IMMUNE CHECKPOINT INHIBITOR–RELATED PNEUMONITIS

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Background: Immune checkpoint inhibitor (ICI)–related pneumonitis is an uncommon but potentially life-threatening toxicity. Reliable biomarkers that predict pneumonitis prior to clinical onset are lacking. We evaluated whether dynamic changes in the neutrophil-to-lymphocyte ratio (NLR) preceding pneumonitis onset are associated with severity.

Methods: Lung cancer patients treated with ICI-based therapy between October 2014 and December 2025 were retrospectively identified from an institutional pharmacy database. Pneumonitis events were graded per CTCAE v6.0 and categorized as mild (grade 1–2) or severe (grade ≥3). Serial complete blood counts were used to calculate baseline NLR and longitudinal pre-onset NLR metrics, including maximum NLR, absolute and percent change, and NLR slopes over 30- and 60-day intervals. Analyses were conducted at the pneumonitis-event level. Group comparisons used Wilcoxon rank-sum tests. Discriminatory performance was assessed using receiver operating characteristic (ROC) analysis, and associations with severe pneumonitis were evaluated using logistic regression. An optimal NLR slope threshold was identified by ROC analysis to define pre-event inflammatory acceleration.

Results: Among 450 ICI-treated patients, 31 patients experienced 38 pneumonitis events (21 mild, 17 severe). Baseline NLR did not differ between mild and severe pneumonitis (median 3.99 vs 4.76; p=0.21). In contrast, severe pneumonitis was associated with higher maximum NLR, greater absolute and percent increases in NLR, and steeper pre-event NLR slopes (all p<0.01). The 30-day pre-event NLR slope was significantly higher in severe compared with mild pneumonitis (median 0.22 vs 0.02 units/day; p=0.001). ROC analysis demonstrated good discrimination for severe pneumonitis (AUC 0.80) and identified a slope threshold of 0.04

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units/day, which detected pre-event NLR acceleration in 94.1% of severe pneumonitis with a median of 15.5 days (IQR 37.3) and in 52.4% of mild pneumonitis with a median of 16 (IQR 28.5) days prior to diagnosis. Each 0.1-unit/day increase in the 30-day NLR slope was associated with increased odds of severe pneumonitis (OR 1.68, 95% CI 1.15–3.18).

Conclusions: Short-term pre-onset increases in NLR, particularly 30-day slopes, identify patients at increased risk for severe ICI-related pneumonitis. Longitudinal NLR monitoring may support earlier risk stratification and proactive clinical management, warranting prospective validation.

Lay Language Abstract: Immune checkpoint inhibitors are powerful cancer treatments, but in some patients they can cause serious lung inflammation called pneumonitis. In this study, we found that a simple blood test marker—the neutrophil-to-lymphocyte ratio (NLR)—often rises quickly in the weeks before severe pneumonitis develops. Monitoring these changes over time may help doctors identify high-risk patients earlier and intervene before the condition becomes life-threatening.