
## 18th Annual Spotlight on Early Career Investigators: A Cancer Research Mini-Symposium

## Thursday, April 25, 2024

## Education Building

# ABSTRACTS

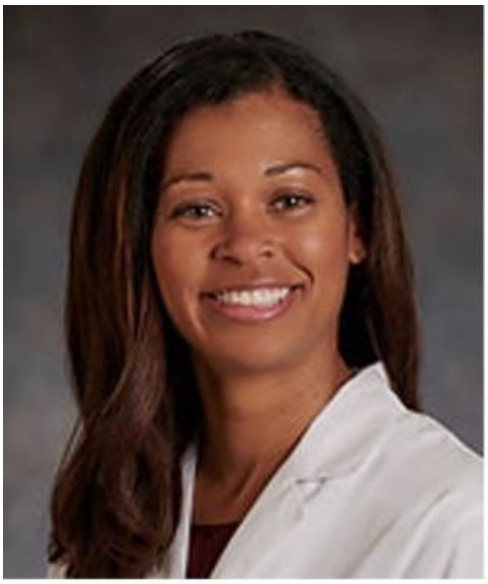
## Contents

## KEYNOTE ADDRESS

**“IF YOU LET ME PLAY, PARALLELS IN SPORTS AND SCIENCE”**

Janai Carr Ascher, M.D., Ph.D., Associate Professor, Cancer Molecular Biology, University of California, Davis, School of Medicine

Dr. Carr-Ascher will discuss her journey in science and how she arrived at cancer biology. She will focus her presentation on the opportunities and the challenges and how skills from sports can be translated into science and medicine.



**Janai Carr-Ascher, M.D., Ph.D.,** is Associate Professor of Medicine at the University of California (UC) Davis School of Medicine at the Comprehensive Cancer Center and serves at the Associate Director for the Education, Training and Career Development.

Dr. Carr-Ascher's research focuses on understanding the biology of sarcoma with the goal of identifying new treatment options. She is working to characterize new ways of studying sarcoma development and metastasis. She is a member of the American Society of Clinical Oncology and the American Society of Hematology.

# Oral Presentation Abstracts

## 1. A NEW VULNERABILITY TO BET INHIBITION DUE TO ENHANCED AUTOPHAGY IN BRCA2-DEFICIENT PANCREATIC CANCER

Suyakarn Archasappawat, Microbiology and Molecular Genetics; EunJung Lee, Department of Microbiology and Molecular Genetics, University of California, Davis; Keely Ji, Department of Microbiology and Molecular Genetics, University of California, Davis; Jocelyn Pena, Department of Molecular Medicine, UF Scripps Institute; Virneliz Fernandez Vega, Department of Molecular Medicine, UF Scripps Institute; Ritika Gangaraj, Department of Chemical Engineering, University of California, Davis; Nitin Sai Beesabathuni, Department of Chemical Engineering, University of California, Davis; Martin Jean Kim, Department of Microbiology and Molecular Genetics, University of California, Davis; Qi Tian, Department of Microbiology and Molecular Genetics, University of California, Davis; Priya Shah, Department of Microbiology and Molecular Genetics, University of California, Davis; Louis Scampavia, Department of Molecular Medicine, UF Scripps Institute; Timothy Spicer, Department of Molecular Medicine, UF Scripps Institute; Chang-il Hwang, Department of Microbiology and Molecular Genetics, University of California, Davis

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the United States, with the lowest five-year survival rate of all cancers. Around 10% of pancreatic cancer diagnoses are thought to be familial pancreatic cancer (FPC). BRCA2 pathogenic variants have been identified to be closely associated with FPC. Personalized medicine approaches that are tailored to FPC patients based on their mutation profiles could improve patient outcomes and minimize adverse effects. This study aims to identify novel potential drug candidates for BRCA2-deficient PDAC and dissect its underlying molecular mechanisms. To discover new vulnerabilities for BRCA2-deficient pancreatic cancer, we performed high-throughput drug screening (HTS) using isogenic murine Brca2 knockout (KO) and control PDAC cells. The HTS assay revealed that JQ1, a small molecule inhibitor of the bromodomain and extra-terminal domain protein (BET) family, selectively induced cytotoxicity in Brca2 KO cells. JQ1 significantly decreased the cell viability of Brca2 KO cells in vitro and suppressed the growth of Brca2 KO tumors in vivo compared to the controls. The transcriptomic analyses showed that JQ1 treatment resulted in upregulation of the gene sets associated with macroautophagy. Multi-orthogonal autophagy assays, including live cell imaging of fluorescence-based autophagy reporter, also supported that Brca2 KO cells had a constitutively higher basal level of autophagic activities compared to the controls, and JQ1 further induced autophagic flux in Brca2 KO cells. Moreover, blocking the autophag¬y process by pharmacological inhibition or knocking down essential autophagy genes rescued JQ1-induced cell death in Brca2 KO cells, indicating that the increased autophagy is responsible for JQ1-mediated cell death in Brca2 KO cells. In conclusion, we found that BRCA2 deficiency elevated autophagic flux, and extensive autophagy was further activated by BET inhibition, culminating in autophagy-dependent cell death in Brca2-deficient pancreatic cancer cells. Our findings suggest that BET inhibition could be a promising therapeutic strategy for treating BRCA2-deficient pancreatic cancer.

## 2. THE EFFECT OF BODY MASS INDEX ON BREAST CANCER STAGE AND BREAST CANCER-SPECIFIC SURVIVAL: A CALIFORNIA CANCER REGISTRY STUDY

Alyssa Bellini, M.D., Department of Surgery, University of California, Davis; Theresa Keegan Ph.D. University of California, Davis Comprehensive Cancer Center; Qian Li, Center for Oncology Hematology Outcomes Research, Training (COHORT) and Division of Hematology and Oncology, University of California, Davis; Frances Maguire Ph.D., University of California, Davis, Cancer Reporting and Epidemiologic Surveillance Program; Victoria Lyo M.D. University of California, Davis, Department of Surgery; Candice Sauder M.D., Department of Surgery, University of California, Davis

Background/Objective

While women with a body mass index (BMI) > 30 kg/m2 or <18.5 kg/m2 diagnosed with breast cancer (BC) are known to have decreased overall survival, the exact mechanisms are unknown, as prior studies evaluating the association between BMI and BC stage were done more than a decade ago and have conflicting results. We aim to further define the relationship between BMI, stage at breast cancer diagnosis, and BC-specific survival. Methods Women age >15 years diagnosed with BC between 2014-2019 were identified from the California Cancer Registry. BMI at diagnosis was classified as underweight (<18.5 kg/m2), normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), obesity class 1-2 (30-39.9 kg/m2), and obesity class 3 (severe obesity) (>40 kg/m2). Due to the high proportion of missing BMI (36.5%), a multivariate imputation by fully conditional specification methods was performed. Late stage at diagnosis was defined as American Joint Committee on Cancer (AJCC) stage 3 and 4. Multivariate logistic regression compared sociodemographic and clinical factors associated with late stage at diagnosis. Multivariable Cox proportional hazards regression models assessed associations of BMI with BC-specific survival, while controlling for sociodemographic and clinical factors; deaths from other causes were considered as competing risks. Results Of 159,318 patients: 2.2% were categorized as underweight, 24.5% normal weight, 30.5% overweight, 26.7% obesity class 1-2, and 6.0% obesity class 3. Patients with severe obesity, compared to normal weight, were more likely to be diagnosed late-stage ($p<0.0001$). The association between BMI and BC-specific survival differed by age ($p<0.0001$). When stratified by age (see Table 1), underweight compared to normal weight patients had worse BC specific survival in the 40-50 and >50 age groups. Patients >50 years with obesity class 1-2 had better BC specific survival, but this association was not observed in the younger age groups. Conclusions

Using population-based data, we observed that severe obesity was associated with a later stage at diagnosis, but not inferior BC survival, as found previously. Instead, underweight was associated with worse survival and indicates a high-risk group.

## 3. THE MULTIFARIOUS ROLES OF ANGEL2 IN CANCER

Christopher Lucchesi, Ph.D., School of Medicine, University of California, Davis, Department of Veterans Affairs; Saisamkalpa Mantrala, Veterans Affairs (VA)-Northern California Healthcare System; Paramita Ghosh, Department of Urologic Surgery, UCD and Veterans Affairs (VA)-Northern California Healthcare System; Xinbin Chen, Veterinary Medicine, Department of Surgical & Radiological Sciences, University of California, Davis; Jin Zhang, Veterinary Medicine, Department of Surgical & Radiological Sciences, University of California, Davis

ANGEL2, which functions as a 2',3'- cyclic phosphatase, is an understudied gene with no known cancer relevant functions. Analysis of the GTEx and TCGA databases revealed that across 17 different cancer types, loss of ANGEL2 was correlated with worse patient prognosis and survival. Specifically, we uncovered that ANGEL2 is a novel, bladder cancer (BlCa) relevant RNA-binding protein. Comparison of ANGEL2 expression between normal

bladder tissue and BlCa tissue demonstrated that ANGEL2 expression was significantly lower in BlCa. Further, ANGEL2 expression decreased significantly in muscle invasive compared to non-muscle invasive bladder cancer (T4 vs T1) implying that loss of ANGEL2 may drive BlCa progression. Analysis of the Gene Expression Profiling Interactive Analysis 2 database uncovered that low ANGEL2 expression is correlated with poor BlCa patient survival and an integrated pan-cancer gene expression and drug sensitivity analysis revealed that ANGEL2 expression was a marker for chemosensitivity. Our preliminary studies demonstrate a potential role for ANGEL2 in modulating translation through its interaction with multiple eukaryotic translation initiation factors and regulating metabolism through its interaction with various metabolic proteins including citrate synthase. Further, loss of ANGEL2 was associated with chemoresistance, increased mobility and stemness markers, upregulation of epithelial-mesenchymal transition markers, and increased metabolic activity. Finally, we show that loss of ANGEL2 increases tRNA-derived RNA fragment accumulation, a novel class of non-coding RNAs whose aberrant expression has been found to participate in cell proliferation, invasive metastasis and progression, and in metabolism in several human malignancies. Taken together, these analyses indicate that ANGEL2 is a multifaceted, understudied gene with a potentially significant role in BlCa progression and treatment response that has yet to be elucidated.

**4. INTEGRIN ALPHA 4 EXPRESSION AS A MARKER FOR RESPONSE TO A NOVEL CTLA-4 INHIBITOR**
**ONC-392)**

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Background: Integrins are a family of surface receptors that mediate interaction between cells and induce signaling across the cell membrane that can regulate cellular migration, activation, and proliferation, particularly in the immune system. Here, we examine the dynamics of integrin expression in peripheral blood mononuclear cells (PBMC) as potential markers for a successful immune response during cancer immune-blockade therapy.

Methods: We generated both single-cell RNAseq (n = 20) and bulk RNAseq (n = 44) transcriptional profiles from the PBMC isolated before and after ONC-392 (a novel CTLA-4 inhibitor) treatment mainly from non-small cell lung cancer adenocarcinoma patients as part of the PRESERVE-001 study (NCT04140526). From the scRNAseq cohort we generated transcriptomes from 138,444 cells. Patients were determined to be responders (R) or non-responders (NR) after 3 cycles of treatment.

Results: We performed a single-cell differential analysis of the integrins before and after treatment and across the major T cell subsets. We found that ITGA4 expression significantly increased after treatment in responders (n = 7) in CD4+ central memory T cells (TCM), T regulatory, and CD8+ T effector memory cells. While ITGA4 expression decreased or was not significantly changed in NR patients (n = 3) in the same cell types. Furthermore, ITGA4 expression with CD4+ TCM correlates with genes enriched for cell activation pathways. A

ITGA4-high cell cluster of CD4 TCM was found to uniquely express PRF1, GZMA, and KLRB1, suggesting a cytotoxic CD4 T cell phenotype and function.

Conclusion: Here we show that integrins, in particular ITGA4, are significantly associated with a successful response to immunotherapy blockade in this small exploratory cohort. ITGA4 has previously been shown to be an important marker of antigen-specific T cell activation and our data here suggests it may be a marker for tumor-specific T cell activation in the context of immunotherapy response. Further studies with a larger cohort are warranted to confirm our findings.

**5. CANCER INCIDENCE AND SURVIVAL AMONG THE ARMENIAN POPULATION IN CALIFORNIA: CONSTRUCTION OF THE ARMENIAN SURNAME LIST (ASL) AND ITS APPLICATION IN THE CALIFORNIA CANCER REGISTRY (CCR)**

Ani Movsisyan Vernon, Ph.D., M.S.A., Department of Public Health Sciences, University of California, Davis Comprehensive Cancer Center, University of California, Davis; Jeffrey S. Hoch, Ph.D., Department of Public Health Sciences; Laura Fejerman, Ph.D., M.Sc.A., A, Department of Public Health Sciences, University of California, Davis Comprehensive Cancer Center, University of California, Davis; Theresa H. Keegan, Ph.D., M.S.A., A. Department of Public Health Sciences, University of California, Davis Comprehensive Cancer Center, University of California, Davis.

Introduction: While California is home to the largest population of Armenians, the categorization of Armenians as 'White' or 'Some Other Race' in population databases has precluded cancer research on this population, despite possible differences in genetic and sociodemographic factors affecting cancer incidence and survival. Purpose: To construct and evaluate an Armenian Surname List (ASL), use the ASL to identify Armenian cancer patients in the California Cancer Registry (CCR), and compare cancer incidence, stage at diagnosis and survival between Armenians and non-Hispanic Whites (NHW) in California. Methods: We extracted Armenian surnames from the Middle-Eastern Surname List and used California death records to construct the ASL and used the ASL to identify Armenians with cancer. For ten common cancers among Armenians, we calculated proportional incidence ratios (PIR) and incidence rate ratios (IRR) compared with NHWs. For four tobacco-related cancers (stomach, lung, colorectal, and bladder) we compared late-stage at diagnosis and cancer-specific survival.

Results: We identified 27,212 Armenian cancer patients. Armenian males had higher proportions of stomach (PIR=2.39), bladder (PIR=1.53), colorectal (PIR=1.29), lung (PIR=1.16), leukemia (PIR=1.16), liver and IBD (PIR=1.19), and kidney (PIR=1.11) cancers. Armenian females had higher proportions of stomach (PIR=3.24), thyroid (PIR=1.47), colorectal (PIR=1.29), pancreatic (PIR=1.20), leukemia (PIR=1.20), NHL (PIR=1.15), and ovarian (PIR=1.14) cancers. Exploratory IRR analyses showed higher stomach (IRR=1.78), bladder (IRR=1.13), and colorectal (IRR=1.12) cancers among Armenian males and higher stomach (IRR=2.54) cancer among Armenian females. Among Armenians, we found higher odds of late-stage colorectal (OR=1.12), lung (OR=1.26), and stomach (OR=1.43) cancers, better survival for stomach (HR=0.85), lung (HR=0.86), colorectal (HR=0.82), and bladder (HR=0.87) cancers, an association between lower neighborhood socioeconomic status with late-stage stomach and bladder cancer diagnoses, and an association between public health insurance with late-stage lung, colorectal, and bladder cancer diagnoses. Conclusion: Armenian patients had higher incidence of several cancers, were at higher risk for late-stage diagnoses of tobacco-related cancers and had a moderate survival advantage. Our findings reveal a need for increased access to cancer screening among Armenians. Further research is needed to address risk factors associated with specific cancers and to understand factors associated with the modest survival advantage observed among Armenians in California.

## 6. TARGETING THE SPLICEOSOME IN HIGH-RISK B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Yuki Murakami, M.D., Ph.D., Department of Pediatrics, University of California, Davis, Comprehensive Cancer Center, University of California, Davis; Clifford Tepper, Ph.D., University of California, Davis Comprehensive Cancer Center, Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis; John McPherson, Ph.D., University of California, Davis Comprehensive Cancer Center, Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis; Noriko Satake, M.D., [1]Department of Pediatrics, University of California, Davis, Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis

The outcome of high-risk B-cell acute lymphoblastic leukemia (B-ALL) is poor, with relapse due to treatment-resistant leukemia cells. Our group discovered a unique subpopulation in B-ALL that is resistant to treatment. Transcriptome studies revealed highlighted RNA splicing in this population. Dysregulated splicing is associated with drug resistance and relapse in B-ALL. SF3B1 is a core component of the spliceosome, and its inhibition is therapeutic in many cancers. In this study, we investigated the therapeutic potential of pladienolide B (Plad-B), an SF3B1 inhibitor, in B-ALL.

SF3B1 protein expression was significantly higher in B-ALL cell lines Reh and JM1, and 28 patient-derived xenograft (PDX) samples (14 each for standard- and high-risk), regardless of the risk group, than in normal B-cells and hematopoietic stem cells. Plad-B showed cytotoxicity in Reh, JM1, and three harvested high-risk PDX samples with IC50 of 0.6-2.2nM. Furthermore, Plad-B, as a single drug treatment, significantly prolonged survival compared to no treatment controls in an Reh xenograft model and a high-risk PDX model (both p<0.01).

G2/M cell cycle arrest and apoptosis were observed 24 hours after Plad-B treatment in the cell lines. RNA-seq examined splicing events in treated Reh at different time points (15, 30, and 60 min). Plad-B demonstrated splicing inhibition as early as 15 min post-treatment and, at 60 min, splicing was inhibited in 1,669 genes. 2,625 differential splicing events were observed in these genes with ~96% from intron retention and exon skipping. 202 genes showed significant changes in their expression, most of which were downregulated, over this time frame. Plad-B induced short pro-apoptotic spliced isoforms, instead of anti-apoptotic forms, in BCL2L1 and MCL-1, downregulated anti-apoptotic genes, BCL-2 and BFL-1, and upregulated a pro-apoptotic gene, BAX, in Reh cells within 24 hours after treatment.

In conclusion, these data demonstrated the therapeutic potential of SF3B1 inhibition in high-risk B-ALL. Plad-B rapidly inhibited splicing in many genes and regulated the BCL-2 family genes, leading to cell apoptosis. In future studies, we will identify the downstream targets of SF3B1 and further investigate the mechanism of rapid apoptosis induction by SF3B1 inhibition.

## 7. A DOSIMETRIC TREATMENT PLAN COMPARISON OF Y-90 RADIOEMBOLIZATION, STEREOTACTIC BODY RADIATION THERAPY, HIGH DOSE RATE BRACHYTHERAPY, AND PROTON BEAM THERAPY FOR LIVER CANCER

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**Purpose**: This study compares four treatment planning modalities on the basis of tumor coverage at prescribed dose, maximum dose delivered to the tumor, and sparing of surrounding organs at risk in order to gain insight for choosing an optimal treatment procedure.

Methods: Seven patients with liver lesions ranging from 8 to 256 mL in volume were treated with Y-90 microspheres; dosimetry was performed using post-treatment PET/CT scans. Structures of interest were delineated on pre-treatment CT images; this includes the liver, gross tumor volume, and relevant organs at risk. SBRT and Proton Beam Therapy four-fraction treatment plans were simulated using RayStation software. Dose for all modalities was converted to Biologically Effective Dose (BED) in order to provide a fair comparison and dose-volume histograms were generated. A prescribed dose of 150 Gy BED was chosen for analysis, which corresponds to a typical SBRT treatment with 4 fractions of 15 Gy physical dose delivered to the tumor target.

**Results**: Y-90 radioembolization treatment resulted in highly variable tumor coverage at prescribed dose, averaging below 50%. Local tumor dose exceeded 2000 Gy. Brachytherapy allowed higher tumor coverage compared to Y-90 and had the highest maximum dose, reaching 4000 Gy. Dose to surrounding tissue was low for Brachytherapy, especially for organs away from the tumor. SBRT and Proton Beam Therapy both offered excellent coverage at prescribed dose. SBRT had a higher maximum dose compared to Proton therapy (209 vs 176 Gy average), but also delivered the most dose to surrounding tissue.

**Conclusion**: All four studied modalities are viable, given careful planning procedures. Y-90 radioembolization allows high local dose, but its distribution is unpredictable. Brachytherapy allows the highest local dose and preserves organs far from the tumor at the cost of invasive administration. Proton Beam Therapy and SBRT offer excellent coverage at prescribed dose with a predictable delivery with Proton taking a slight edge in coverage and sparing of organs at risk.

# Poster Presentation Abstracts

## 1. FLUORESCENCE LIFETIME SIGNATURES OF COLORECTAL POLYPS: A FEASIBILITY STUDY

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Colorectal cancer is the third most diagnosed cancer and the second leading cause of cancer-related deaths worldwide. A critical problem in the early detection of colorectal cancer is that conventional methods (e.g., white light endoscopy) may not readily distinguish malignant from benign tissue in real-time. We hypothesize that normal colorectal tissue, pre-cancer, and cancerous lesions display distinct fluorescence properties (i.e., intensity and lifetime) due to differences in metabolism and structure. Such contrast could be potentially resolved with interventional fluorescence lifetime imaging (FLIm) for real-time in situ biochemical information that could enhance the efficacy of colonoscopy procedures.

## 2. STRUCTURE-FUNCTION ANALYSIS OF THE BRCA2 TUMOR SUPPRESSOR PROTEIN

Carolin Aurich, Department of Microbiology and Molecular Genetics, University of California, Davis; Hang Phuong Le, Department of Microbiology and Molecular Genetics, University of California, Davis; Jie Liu, Department of Microbiology and Molecular Genetics, University of California, Davis; Wolf- Dietrich Heyer, Ph.D., Department of Microbiology and Molecular Genetics, University of California, Davis

The tumor suppressor gene BRCA2 ensures the integrity of an organism's genome and suppresses breast, ovarian, prostate, pancreatic and other cancers. BRCA2 functions in multiple genome stability pathways: homologous recombination (HR), replication fork stabilization, single-stranded DNA (ssDNA) gap suppression, and regulation of DNA polymerase θ ( POL θ) mediated end joining. In the past, researchers have described several clusters concentrated with mutations, that appeared to be linked to either breast, ovarian, or pancreatic cancers. However, it is unclear whether these clusters reflect functional specialization in the respective tissues or are a consequence of limited data availability at the time. To address this question, we analyzed the ClinVar dataset, a public archive of cancer-relevant mutations. Our analysis revealed that mutational clusters are associated with structural and functional domains of BRCA2 but not specific tumor types. Additionally, we identified a hotspot for all types of mutations in the C-terminal helical domain of BRCA2, which has no known function. Our future aim is to prepare and characterize BRCA2 mutants deleting the helical domains to define its function and improve the mechanistic understanding of this important tumor suppressor.

## 3. CELL-FREE EXPRESSION AND REFOLDING OF MEMBRANE PROTEINS

Gregory Bude, Lawrence Livermore National Laboratory; Joshua Claxton, Lawrence Livermore National Laboratory; Mariam Mohagheghi, Lawrence Livermore National Laboratory; Matt Coleman, Lawrence Livermore National Laboratory; Shakiba Nikfarjam, Lawrence Livermore National Laboratory

Expressing and refolding membrane proteins pose significant challenges, especially in cell-free systems. While conventional methods like solubilization within nanolipoprotein particles (NLPs) are applicable for some proteins, they have limitations for specific targets. In this study, we introduce an innovative strategy using novel synthetic polymers, particularly styrene maleic acid copolymers (SMALPs), along with lipids for solubilizing and refolding membrane proteins within nanodiscs. Our method involves expressing membrane proteins, including the Major Outer Membrane Protein (MOMP) of Chlamydia trachomatis, CAR-T receptors, and the Receptor Binding Domain (RBD) of the Spike protein from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), in

Escherichia coli cell-free lysate. Following expression, protein pellets are solubilized in 1% SDS and then refolded in lipids extracted from bovine heart and soy. Incorporating SMALPs enhances protein stability within synthetic nanodiscs, improving solubility and functionality. Our results demonstrate robust yields of refolded protein, typically ranging from 300-500 microliters of 0.25mg/mL protein of interest. The lipid refolding technique, involving multiple centrifugation and wash steps, yielded relatively pure products even without additional purification requirements. However, methods such as flag or histag purification can further increase purity. Compared to traditional NLP solubilization methods, our approach shows increased compatibility with cell-free expression systems and significant improvements in protein-nanodisc formation for all three target proteins. Functional validation confirms successful refolding, demonstrated through conformational antibody recognition and dot blotting. In summary, our novel cell-free methodology offers a streamlined approach for expressing and solubilizing challenging membrane bound receptors to advance the production of clinically relevant therapeutic proteins.

## 4. GENERATION OF A CAR T RECEPTOR SUPPORTED IN A NANOLIPOPROTEIN COMPLEX FOR IMMUNOTHERAPY

Joshua Claxton, Lawrence Livermore National Laboratory, Gregory Bude, Lawrence Livermore National Laboratory

CAR-T therapies have shown the ability to defeat several blood-borne cancers including advanced leukemias and lymphomas. However, these approaches are costly and time-consuming. New technologies are needed for generation and formulation that are low-cost and simple. Nano lipoproteins (NLPs) have shown promise in their ability to solubilize proteins and allow them to fold properly and preserve function as well as being amenable to low-cost production. We have utilized the Chimeric Antigen Receptor (CAR) to create functioning “CAR-NLPs” with the intention that they can provide a versatile tool for studying target interaction and a provide a platform for the next generation of CAR constructs in the future. CAR-CD1928z binds to the CD19 receptor that is highly expressed in cancer cells and causes T-cell induction and targeted cell death. To develop a faster and more robust platform we used cell-free expression to generate a CAR-CD1928z receptor, which was solubilized within the NLP formed by the Δ49Apolipoprotein A1 scaffold protein in the presence of lipids. When the CAR protein is expressed in the absence of these NLP scaffold components, we found little to no soluble protein in solution, therefore we then optimized the production of the CAR-NLP complex using a series of temperature and lipid screens to determine the ideal environment that optimized expression, purity and solubility. We found through gel electrophoresis densitometry analysis, that running a Cell Free reaction at 20˚C for 24 hours produced up to 82% solubilized CAR protein. The association between the CAR-CD1928z receptor and the NLP was confirmed by nickel affinity purification using a His tag on the Δ49Apolipoprotein A1 component. Once we established the complex, we tested solubility and functionality using CART-specific antibody binding assays. The CART-specific antibody binding assays included Western and Dot Blots. We further show how we can go from generation through functional characterization and application in under three days. Overall, this is an exciting first demonstration of CART formulations utilizing NLPs, which may help to lower the time and cost of novel immune-therapeutic formulations.

## 5. CHARACTERIZING PARP INHIBITOR AND NEXT-GENERATION ANTI-ANDROGEN RESPONSES IN ADVANCED PROSTATE CANCER

Bryan Correa Gonzalez, Biochemistry and Molecular Medicine, University of California, Davis; Love A. Moore, University of California, Davis; Alan P. Lombard, Department of Biochemistry and Molecular Medicine, Department of Urologic Surgery, University of California, Davis

Treating metastatic castration-resistant prostate cancer (mCRPC) with poly (ADP-ribose) polymerase inhibitors (PARPi) has been effective in men harboring mutations in DNA repair genes. Success has been seen when combining PARPi’s with next-generation anti-androgen therapies (NGAT), another mCRPC treatment. Previous work has demonstrated that PARP inhibition leads to both cell death and senescence. It is unknown if NGATs act as a senolytic, which induce death of senescent cells. We hypothesize that combining PARPi’s with a senolytic enhances PARPi efficacy, driving tumor cells towards apoptosis. In this study, we sought to characterize the

combination of NGAT's and a PARPi to determine if the combination would promote synergism and a synthetic lethality effect. To test the hypothesis: cell growth assays and cell morphology were analyzed in cells lines C4-2B, MDVR, and Abi-R. Cell lines C4-2B, MDVR, and AbiR were treated with: DMSO as a control, monotherapies of NGAT's (Enzalutamide or Abiraterone), and a PARPi (Olaparib or Talazoparib) as well as the respective combinations. As expected, drug combinations were more efficacious at limiting cell growth than either monotherapy. Although the combinations were found to reduce cell growth, cells appeared more cytostatic than apoptotic. Our work suggests that combining PARPi's with NGAT's doesn't promote cell death but a persistent cytostasis which may allow tumor progression and resistance. Future studies are directed at further characterizing combinations with PARPi's and developing novel strategies to enhance their efficacy.

## 6. EFFECTS OF SHORT- AND LONG-CHAINED PFAS ON TRIPLE NEGATIVE BREAST CANCER PROGRESSION

Hector Delgadillo, Department of Environmental Toxicology, University of California, Davis; Shenq-Shyang Huang, Department of Environmental Toxicology, University of California, Davis; Aman Singla, Department of Environmental Toxicology, University of California, Davis; Hidetoshi Mori Pathology and Lab Medicine, University of California, Davis; Michele A. La Merrill, Department of Environmental Toxicology, University of California, Davis

Per- and polyfluoroalkyl substances (PFAS) are a class of compounds commonly used as surfactants in food contact materials and household items due to their hydrophobicity. However, their physicochemical properties render them highly resistant to degradation in the environment and human body. Thus, these chemicals are environmentally ubiquitous and are estimated to be found in the serum of 98% of U.S. citizens. Additionally, evidence shows PFAS are linked to cancer progression and endocrine disruption, though the mechanisms remain unclear. This research analyzes and compares the effects of four PFAS of varying alkyl chain lengths on breast cancer progression in vitro. Using the aggressive human cell line Hs578T the effects of four PFAS are analyzed across environmentally relevant doses. Progression is assessed through "2.5D" culture assays using Matrigel. Results show no significant increases in colony formation with increasing PFAS dose. Significant increases in colony formation were not observed with increasing alkyl chain length but a clear, significant increasing trend exists. The results will help us better understand whether breast cancer progression is related to dose and alkyl chain length, and whether short-chain alternatives exhibit increased progression as other PFAS have been shown to promote.

## 7. IDENTIFYING FORCE-DEPENDENT PROTEIN INTERACTIONS SURROUNDING ACTIN FILAMENTS

Agustina Diener, Biomedical Engineering, University of California, Davis, Hikaru Katani, Kyoto University, Yurina Araki, Osuka University, Volkmar Heinrich, Ph.D., Biomedical Engineering, University of California, Davis, Soichiro Yamada, Biomedical Engineering, University of California, Davis

Mechano-transduction is the process by which a cell senses, integrates, and converts mechanical stimuli into biochemical signals, thereby regulating cell adhesion and cell behavior including cancer progression. Yet, the molecular details of this process are not well understood. Upon physical stimulation, actin filaments recruit vital regulatory proteins to initiate mechano-transduction, the comprehensive list of proteins surrounding the "tensed" actin network has not been described. To identify force-dependent protein interactions surrounding actin filaments, we fused TurboID, a promiscuous biotin ligase, with F-tractin, an actin filament binding sequence. Using purified biotinylated samples from control and stretch conditions, our preliminary mass spectrometry analysis identified over 1000 of proteins and these proteins were ranked based on the relative abundance of proteins in the stretch and control samples. As expected, Zyxin and ABLIM1, LIM proteins which are known to bind to strained actin filaments, and ACTN1, an actin binding protein that is known to interact with zyxin, were identified as proximal to the tensed actin network. Interestingly, LATS1, a tumor suppressor, was also among the top candidates, but not known to be a part of mechano-transduction. LATS1 proteins appear to partially colocalize with the keratin network upon stretch, thus demonstrating close proximity of the actin and keratin network. By identifying force-sensing proteins, we will better understand the molecular basis of mechano-transduction, and may uncover the potential role of this process in cancer.

## 8. REDUCED T-CELL RECEPTOR DIVERSITY IS NOT DIAGNOSTIC FOR INTESTINAL LYMPHOMA IN CATS

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Senior cats often suffer from chronic enteropathy (CE), encompassing inflammatory bowel disease (IBD) and intestinal lymphoma. Affected cats present with vomiting, diarrhea, and weight loss, often culminating in euthanasia. The gold standard for diagnosing intestinal lymphoma involves demonstrating a reduced T cell receptor (TCR) diversity in intestinal biopsies using clonality testing. This project aimed to characterize TCR diversity in cats. We hypothesized that 1) TCR diversity decreases with age and 2) there is no significant difference in TCR diversity between cats with and without CE. DNA was extracted from formalin-fixed and paraffin-embedded intestinal biopsies from 50 cats with and without CE, the hypervariable region of the TCR gene was amplified by PCR and TCR diversity was scored semi-quantitatively (from 1/low to 4/high). Results showed that TCR diversity decreased with age and that this decrease was most notable in cats older than 10 years. Unexpectedly, cats with CE had a higher mean diversity score than cats without CE (2.9 vs. 2.7) but this difference was not statistically significant. These findings suggest that low TCR diversity could, in part, represent an age-related change and that it is not indicative of intestinal lymphoma in call cases.

## 9. REDUCING DISPARITIES IN HEREDITARY BREAST CANCER RISK ASSESSMENT - THE 'TU HISTORIA CUENTA' PROGRAM

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Hispanic/Latina (H/L) women in the United States have a 30% higher risk of breast cancer mortality compared to non-Hispanic White women. This is partly due to lower screenings and genetic counseling/testing rates. To address this disparity, we developed a program that identified, tested, and counseled H/L women at high risk of developing breast cancer in Los Angeles, San Francisco, and Sacramento. Community health educators were trained to outreach, educate, and survey participants. A validated survey collected the cancer-related family history of each participant. Individuals with a positive or uncertain result underwent genetic counseling. Barriers to successful participation in genetic testing included loss to follow-up and difficulties during the kit activation or interpretation of the results. These barriers can be addressed by providing one-on-one support to participants throughout the process.

## 10. EVALUATION OF INHALED IL-15 THERAPY AND IL-8 IN CANINE OSTEOSARCOMA

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The primary cause of treatment failure and death in osteosarcoma (OS) patients is lung metastasis. There is an urgent need to evaluate strategies that combat the early establishment and outgrowth of lung metastases to improve outcomes in OS patients. In a naturally occurring canine model of advanced-stage OS, we have demonstrated that inhaled rhIL-15 treatment yields clinical responses in a minority of patients; however, preliminary results from an ongoing trial indicate that inhaled rhIL-15 accelerates lung metastasis in early-stage OS when in combination with standard-of-care amputation and chemotherapy. Interestingly in the first phase I trial, while systemic exposure to IL-15 4 hours post inhaled rhIL-15 was low (~40 pg/mL), there was a significant increase in plasma IL-8 (~5000 pg/mL), a pro-inflammatory cytokine tied to increasing lung metastasis in human OS mouse models. In this current study, we have investigated the role of IL-8 in the progression of canine OS in vitro and the potential link between IL-15 and IL-8. Canine OS cells were found to express varying baseline and inducible—by TNFa (10 ng/mL)—levels of IL-8. Surprisingly, based on qPCR and functional assays, canine OS cells were found to not express the receptors for IL-8, CXCR1 or CXR2. Correspondingly, IL-8 does not have a direct impact on canine OS proliferation or migration as previously expected. Further, rhIL-15 was not demonstrated to increase IL-8 production from canine OS cells in vitro. However, canine PBMCs ex vivo were demonstrated to produce higher levels of IL-8, TNFa, and IFNy when treated with rhIL-15 and conA. Overall, these results have spurred our current hypothesis that IL-15 indirectly induces IL-8 production of canine OS cells, and canine OS cell derived-IL-8 plays a pro-metastatic role in canine OS through regulating the lung microenvironment. (Funding: NHLBI Comparative Lung biology and Medicine T32 fellowship)

## 11. RURAL-URBAN AND RACIAL AND ETHNIC DISPARITIES IN INVASIVE MELANOMA, A POPULATION-BASED RETROSPECTIVE COHORT STUDY.

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Importance: Disparities exist in melanoma incidence across rural/urban and racial/ethnic continua, but few studies have examined the overlap of these factors. For a malignancy that is curable if detected early, identifying these disparities may inform public health initiatives and improve patient outcomes.

Methods: Patients diagnosed with invasive cutaneous melanoma during 2000-2019 were identified from the United States Surveillance, Epidemiology, and End Result database. Rural/urban residence was determined by Rural Urban Commuting Codes. Race and ethnicity were classified as Hispanic (all races), Non-Hispanic American Indian/Alaska Native (NHAIAN), Non-Hispanic Asian/Pacific Islander (NHAPI), Non-Hispanic Black (NHB), and Non-Hispanic White (NHW). Age-adjusted incidence rates (IR, per 100,000) by rural/urban residence and race and ethnicity were calculated. Incidence rate ratios (IRRs) compared incidence between rural and urban residence. Results: 484,841 cases of melanoma from 2000-2019 were assessed. IR from 2010-2019 was lower

in rural than urban NHAIAN patients (6.4 vs 8.6; IRR: 0.74; 95% CI: 0.59 - 0.91) and NHW patients (26.3 vs 30.8; IRR: 0.85; 95% CI: 0.84 – 0.86). By contrast, IR was higher in rural than urban NHAPI patients (3.1 vs 1.3; IRR: 2.4; 95% CI: 1.9 – 3.0). A similar pattern was observed during 2000-2009. No significant differences in rural/urban residence IR were found for Hispanic and NHB patients.

Conclusions: Melanoma incidence in NHW patients is dramatically higher than in other groups, but the relationship between incidence and rural/urban residence appears to differ by race and ethnicity. Additional studies, controlling for key sociodemographic and cultural factors, are needed to determine the mechanisms through which rural/urban residence influence melanoma risk in specific populations.

## 12. ROSE+: RAPID ADEQUACY AND DIAGNOSTIC DETERMINATIONS FOR CORE-NEEDLE BIOPSY SPECIMENS USING FIBI-ENABLED SAMPLE-SPARING SLIDE-FREE HISTOLOGY

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Histological diagnoses obtained through minimally invasive biopsies are critical to providing timely and accurate diagnoses in oncologic and infectious diseases. Although minimally invasive, needle biopsy procedures pose risks of damaging tissue or blood vessels and inadequate tissue sampling, occurring in over 20% of cases. Traditional histopathology, the gold standard for the diagnosis of these biopsies, is precluded as it requires significant time and care. These factors may result in the need for repeat biopsies and delays in diagnosis, impacting patient care, increasing healthcare costs, and heightening patient anxiety. There is a need for a real-time diagnostic approach for needle-based biopsy procedures of patients with suspected cancer to enhance both diagnostic yields and adequacy confirmation.

Fluorescence Imitating Brightfield Imaging (FIBI) is a technique that bypasses formalin fixation and paraffin embedding (FFPE) processes by capturing images of the surface of non-sectioned, freshly excised specimens to provide histology-grade images within minutes. This novel process addresses concerns of cost, time, and sample adequacy and identification for downstream immunohistochemistry, sequencing, or other molecular analyses. FIBI has demonstrated significant promise in facilitating accurate diagnoses, showcasing clinical concordance rates of 97% when compared to standard slide-based diagnoses.

Our study aims to optimize tissue processing, staining, and handling by evaluating approximately 100 needle biopsy specimens of soft tissue lesions. We anticipate observing the non-inferiority of FIBI images compared to standard FFPE and sectioned H&E images and the superiority of FIBI over diagnoses made through cytological touch prep or concurrent fine-needle aspirations.

13. **THE EFFECTS OF CHRONIC STRESS ON CANCER PROGRESSION AND METASTASIS: AN IN-VITRO BREAST CANCER CELL MODEL.**

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Introduction: In the last decade, rates of chronic stress and triple negative breast cancer (TNBC) have rapidly increased across the world, with historically marginalized communities being particularly affected by both at a higher rate. Several animal models, developed to study the adverse effects of psychosocial stress on cancer have linked stress to cancer progression. However, little is known if such a model can be replicated on a cellular level, especially for the purpose of screening environmental pollutants to look at their potential to affect cellular stress responses. This research aims to create an in vitro TNBC cell model to allow us to investigate the independent and joint effects of chronic stress and environmental chemicals on breast cancer progression, metastasis, and growth. Methods: TNBC cell lines were cultured for 7 days with different levels of free cortisol between 1 and 100nM, reflecting concentrations found in human plasma. RNA was isolated and the expression of known glucocorticoid receptor (GR) target genes was determined. The TNBC cell line Hs578T was chosen for 20-day, long-term culture. Cell population doubling rate was assessed at every passage through Trypan Blue exclusion. DNA and RNA were collected at every passage to assess gene expression; protein and cells were collected at set points for downstream analysis, including the Cyquant cell proliferation assay and invasion assays using Matrigel.Results: The expression of known GR target genes, including FKBP5, GILZ, and SGK1, were significantly elevated in Hs578T cells treated with 100 nM cortisol. Studies using the two-month model with continual dosing of Hs578T cells with vehicle, 1, and 10 cortisol are ongoing. We expect that this model would reflect the cellular responses of chronic stress, distinct from effects observed in response to an acute stressor. Conclusion: We are developing a cellular model for the long-term assessment of how chronic stress affects the progression of breast cancer. This model will help us better understand the role of chronic stress in cancer progression and understand how toxicant burden interacts with chronic stress to exacerbate these effects.

**14. MONITORING ENVIRONMENTAL CONTAMINANTS USING SILICONE WRISTBANDS IN THE YUROK TRIBE**

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Since time immemorial, Yurok People have been stewards of the Klamath River and the surrounding marine and inland ecosystems. The Yurok Indian Reservation (YIR) extends for one mile from each side of the Klamath River, 46 miles from the mouth of the Klamath River to the Pacific Ocean upriver to the town of Weitchpec. .5,30 Yurok traditionally eat salmon, sturgeon, and candlefish from the Klamath River, gather mussels and seaweed from the ocean, and harvest acorns, deer, and elk from inland environments.30 The Yurok reservation is historically near timber mill company operations; statutes including the 1878 Timber and Stone Act facilitated lumber companies' acquisition and exploitation of timber on Yurok ancestral lands. The location of the Yurok reservation, where the river meets the ocean, also makes it a final catchment for any contaminant residues within the Klamath River watershed.30 Silicone wristbands as passive wearable monitoring devices are a unique way to sample environmental contaminants by offering an environmental, time-weighted average concentration over an exposure period, allowing for better detection of human ambient air and dermal contaminants.41,42 Other environmental exposure studies have used silicone wristbands to examine exposure to environmental pollutants from

occupation-specific exposure.43 We have partnered previously with the Yurok Tribal Environmental Department (YTED) on the Yurok Superfund project and will continue our collaboration for the wristband project using community-based participatory research (CBPR) methodology. We have recruited 25 Yurok tribal participants to participate in two study periods, summer, and winter, wearing silicone wristbands for one week while completing a daily activity log. I hypothesize that the Yurok People have a higher environmental contaminant exposure burden than the general population due to their subsistence and cultural activities on the Yurok Reservation. We aim to use silicone wristbands to determine the level of exposure to environmental contaminants among the Yurok Tribal members and describe the potential link between environmental contaminants and adverse health outcomes.

## 15. ELUCIDATING THE ROLE OF YAP IN SARCOMA DEVELOPMENT

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High-grade complex karyotype sarcomas represent a rare and heterogeneous group of tumors. Despite their diverse histological subtypes and molecular profiles, these sarcomas are treated similarly with varying outcomes. Thus, identifying the factors driving high-grade complex karyotype sarcomas will create new targeted therapeutic opportunities. Previously our lab developed a new preclinical model in which human mesenchymal stem cells (MSCs) can transform into multiple subtypes of complex karyotype sarcomas by knockout of the tumor suppressors RB and p53 and expression of an oncogene. Human RB-/-P53+/- MSCs with addition of Yes-associated protein (YAP), an oncogene driver histologically and phenotypically reflects the most common sarcoma subtype in adults, undifferentiated pleomorphic sarcoma (UPS). Further, comparing differential expression analysis from YAP driven tumors and human UPS tumors from the cancer genome atlas (TCGA) revealed upregulation of oxidative phosphorylation pathways. In addition, genetic analysis of tumors formed by other oncogenes including PI3K, which forms osteosarcoma, revealed amplification of YAP. Therefore, we hypothesize that YAP is required for the developments of soft tissue and bone sarcomas and serves as a viable therapeutic target for sarcomas. To test this hypothesis, we first validated our oxidative phosphorylation results by conducting a mitochondrial stress assay and observed YAP could increase oxidative phosphorylation. We then treated five sarcoma cell lines representing multiple subtypes with a complex 1 inhibitor to block oxidative phosphorylation, a YAP inhibitor, or both. From this, we noted a decrease in cell proliferation when treating with either drug and a synergistic effect when treating with both drugs. In addition, using CRISPR we knocked out endogenous YAP and assessed the transformation potential of PI3K in-vitro. We observed that PI3K tumors depend on YAP amplification for survival and proliferation. Sarcoma heterogeneity is multilayered. Apart from patient and histological heterogeneity, intratumoral and intrasubtype heterogeneity is seen in subsets like UPS. Here we demonstrated the feasibility of targeting YAP and oxidative phosphorylation in multiple sarcoma subtypes. Using our osteosarcoma model, we observed amplification of YAP and showed these tumors depend on YAP for survival. These studies support further mechanistic investigations focused on the role of YAP as a driver of sarcoma development and transformation.

## 16. IDENTIFYING CELL-CELL FUSION MACHINERY USING PROXIMAL BIOTINYLATION

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Cell-cell fusion has been observed in cancer development and proposed to play a role in carcinogenesis, cancer metastasis, and resistance to chemotherapy. Epithelial cells do not normally fuse, however, viral fusogen protein p14FAST can activate cell-cell fusion machinery in epithelial cells. So far, few endogenous proteins associated with the pathway of p14FAST-mediated fusion have been discovered. Using Biotinylation IDentification analysis (BioID), proteins proximal to p14FAST before and during cell-cell fusion were detected with mass spectrometry. Actin regulators were identified in pre-fusion cells while transmembrane proteins and membrane regulators were identified in fused and fusing cells. Top candidates were selected and over-expressed in fusing cells to test their effect on cell-cell fusion efficiency. If the candidate protein is involved, perturbation of the protein level may compromise or facilitate fusion efficiency. These newly identified epithelial-specific cell fusion regulators may play a role in cancer cell fusion. Therefore, our study provides the first step in understanding cell-cell fusion mechanisms and potentially determining the endogenous machinery used by cancer cells.

## 17. COLLAGEN AND ELASTIN AS BIOMARKERS FOR STUDYING DISEASE: UTILIZING DUET IMAGING

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Collagen and elastin are prominent components in both normal and abnormal tissues, and their presence and distribution are significant for fibrosis-, cardiovascular- and cancer-related processes. Collagen quantification in the context of fibrosis, often associated with irreparable organ injury, can predict the disease severity and patient prognosis. In cardiovascular research, elastin signatures can be an important factor in better understanding coronary artery disease processes. In cancer care, identifying elastin from patient biopsies can play a significant role in aiding pathologists in their clinical workflow to identify vascular invasion of cancer cells. Traditional methods to quantify collagen and elastin vary in accuracy, cost, and ease of use. Using DUET microscopy on H&E slides, high-resolution collagen and elastin mapping is possible without added staining steps or expensive optical instrumentation. Here, we demonstrate DUET's approach in chronic kidney disease (CKD), coronary artery disease (CAD), and in identifying vascular elastin in colon cancers.

## 18. TANDEM LIM DOMAIN CONTAINING PROTEINS, LIMK1 AND LMO1, DIRECTLY BIND TO FORCE-BEARING KERATIN INTERMEDIATE FILAMENTS

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Invasive cancer cells are constantly exposed to physical forces from surrounding extracellular matrix and neighboring cells, and respond to such mechanical stimuli. Previous studies have implicated LIM-domain containing proteins, often dysregulated in cancer (e.g. LMO1), as mechano-sensing proteins and identified several key requirements for LIM proteins' force-sensitivity. For example, LIM proteins require at least three consecutive LIM domains for efficient recruitment, accumulate along force-bearing actin cytoskeleton, and their tandem LIM domains are solely responsible for this force-induced interaction. However, the precise mechanism of LIM domain's force-induced interactions and their involvement in cancer remain largely unresolved. To investigate and characterize the specific mechano-responses of these LIM proteins, an epithelial cell model was used to screen 18 different LIM proteins across the 14 classes in the protein family. This uncovered surprising interactions with the cyto-keratin network unique to epithelial cells. Our results suggest that LIM domain's mechano-sensing abilities extend beyond the actin cytoskeleton, highlighting the diverse role of LIM proteins in force-regulated signaling. Moreover, the recruitment of signaling proteins like LIMK1 and LMO1 to force-bearing keratin fibers suggest that the keratin network may play a more active role in cells' mechano-resilience. In fact, the keratin network may serve as a better scaffold for force-sensitive signaling in cancer cells, because unlike actin filaments and microtubules, the intermediate filaments can withstand more extreme strains without breaking, therefore may play in important role in cancer cell survival during physically demanding processes like metastasis.

## 19. DNA ADDUCTS DETECTABLE IN LUNG AFTER IN VIVO NAPHTHALENE EXPOSURE

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Humans are frequently exposed to naphthalene, an abundant combustion product and air pollutant that promotes tumor formation in respiratory epithelium of the mouse lung and rat nose. Naphthalene is bioactivated by enzymes in the body to form toxic metabolites. These naphthalene metabolites have been shown to form stable DNA adducts (a potential genotoxic mechanism) in mouse airway explants, but it is unclear if this occurs in vivo, as ex vivo explants do not fully recapitulate a complex multi-organ system. We hypothesized that naphthalene is capable of adducting to DNA in vivo and that DNA adduct quantity would vary by duration after exposure due to the impact of DNA repair mechanisms. Wild-type C57BL/6 mice were exposed to 50 mg/kg 14C-labeled naphthalene or vehicle (corn oil) via oral gavage. Lung lobes were collected at four post-exposure timepoints (2, 4, 24 & 72 hours) and washed with 1x PBS to remove residual external blood. DNA was extracted from lung lobe homogenate, processed into graphene, then analyzed using accelerator mass spectrometry to measure quantities of naphthalene-induced DNA adducts by isotope ratios. Aligned ranks transformation analysis of variance (ART-ANOVA) demonstrated levels of naphthalene-DNA adducts varied significantly across timepoints ($P < 0.001$), with the greatest quantity present at 4 hours post-exposure. One-way analysis of variance (ANOVA) with Tukey's post-

hoc test performed at each respective timepoint showed levels of DNA adducts were significantly elevated above sex-pooled controls at 4 hours ($P<0.05$, both sexes), 24 hours ($P<0.01$ males, $P<0.05$ females), and 72 hours ($P<0.05$, both sexes) after exposure. Detection of naphthalene-induced DNA adducts in vivo following oral exposure at 72 hours post-exposure is of particular concern, as these adducts are persisting beyond the window of DNA repair, and could potentially contribute to genotoxicity in the mouse lung.

## 20. MODELING TORTUOUS VESSEL GEOMETRY FOR PATIENT-SPECIFIC Y-90 RADIOEMBOLIZATION

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Treating cancer patients diagnosed with hepatocellular carcinoma with transarterial radioembolization is increasingly used due to its minimal invasiveness and sparing of adjacent healthy tissues from radiation exposure. The use of complex physics-based modeling techniques with patient-specific clinical data shows much promise to support pre- and post-treatment strategies for improved tumor targeting through high-precision dosimetry. However, radioembolization requires quick clinical decision-making during the Y-90 microsphere injection, leading to challenges in implementing accurate but computationally expensive pre-treatment models. Unfortunately, these models suffer from uncertainty from multiple sources when assumptions are made to speed up the computation. We developed a modeling framework, CFDose, that incorporates clinical patient cone-beam Computed Tomography (CBCT) images and applies physics-based techniques to predict microsphere transport in the patient liver vasculature using computational fluid dynamics (CFD). Radiation dosimetry is then performed from the predicted microsphere transport. We have demonstrated a proof-of-concept and used post-treatment Positron Emission Tomography (PET) imaging of the yttrium-90 microspheres to compare the assess the accuracy of the predicted radiation dose distribution.

The core concept of CFDose is patient-specific modeling based on parameters obtained from clinical data (e.g. images, blood flow, and pressure). Challenges from this physics-based approach stem from adequate calibration, measurement of the required parameters, and validation. In this work, we aim to address uncertainty in the modeling assumptions by considering geometric variations in CBCT-derived images, and their subsequent effect on CFD results. We derived an idealized tortuous vessel inspired by patient-specific CBCT vessel segmentation of the right-hepatic artery and evaluated downstream particle distributions following an ideal catheter centered in the vessel lumen. Three modeling scenarios consider: 1) tortuous vessel geometry truncation, 2) injection position variations along the tortuous vessel, and 3) increased vessel tortuosity injection. Our results show that in all 3 cases, asymmetry in particle distributions can be attributed to the injection position located in areas of increased tortuosity. Additionally, vessel tortuosity can contribute to asymmetric distribution despite being positioned further from the branching bifurcation. This work informs patient-specific CFD simulations and the modeling assumptions that may aid in more accurate dosimetry for TARE procedures.