SPOTLIGHT
ON EARLY CAREER INVESTIGATORS

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Goodnight Auditorium
UC Davis Comprehensive Cancer Center

ABSTRACTS

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KEYNOTE ADDRESS

FROM PASSION TO PROFESSION: PAVING MY OWN PATH IN ONCOLOGY

Mili Arora, MD, Associate Professor, Hematology/Oncology, UC Davis School of Medicine

Dr. Arora will discuss her career path and the lessons learned that have led to her current role as a physician, an educator, and a researcher. She will also review her key research interests and the development of the clinical trial portfolio in breast oncology at UC Davis; her ongoing research in the androgen receptor in advanced breast cancer and the exploration of alternative supportive care to reduce toxicities for breast cancer treatment.

Mili Arora, MD, is Associate Professor of Medicine at the University of California (UC) Davis School of Medicine at the Comprehensive Cancer Center and also serves as the Program Director for the Fellowship Program in the Division of Hematology & Oncology as of August 2021. Her leadership responsibilities also include Chair of the Breast Malignancies Disease Team Committee. Her principal research and clinical interests focus on breast cancer, and she has a specific interest in triple negative breast cancer. She was the 2019 Placer Breast Cancer Foundation Awardee, the 2019 Christine and Helen Landgraf Memorial Research Awardee and most recently the 2021 Safeway Foundation Grant Recipient. She has been on the faculty at UC Davis since 2015.

Dr. Arora was a Clinical Fellow in Hematology/Oncology at UC Davis Medical Center and served as Chief Fellow in 2014. She also completed her Internal Medicine Residency at Tufts Medical Center. Dr. Arora holds an MD from George Washington University and a BS in Biomedical Engineering from Virginia Commonwealth University.

Oral Presentation Abstracts

1. REGULATION OF GENES LOCATED IN 6Q25 BY NON-EUROPEAN GENETIC VARIANTS IN BREAST CANCER PATIENTS FROM PERU

Valentina Zavala, Department of Public Health Sciences, University of California Davis, Davis, CA; Xiaosong Huang, Department of Public Health Sciences, University of California Davis, Davis, CA; Sandro Casavilca-Zambrano, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Jeannie Navarro-Vásquez, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Ruddy Liendo-Picoaga, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Monica Calderón, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Guillermo Valencia, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Henry Gómez, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Patricia Rioja, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Carlos A. Castañeda, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Zaida Morante, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Silvia P. Neciosup, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Hugo A. Fuentes, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Julio E. Abugattas, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Jose M. Cotrina, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Katia Roque, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Jule Vásquez, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Luis Mas, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Marco Gálvez-Nino, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Jovanny Zabaleta, Department of Pediatrics and Stanley S. Scott Cancer Center; Michelle Williams, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; Bizu Gelaye, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; Tatiana Vidaurre, Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; Laura Fejerman, Department of Public Health Sciences, and UC Davis Comprehensive Cancer Center, University of California Davis, Davis, CA

Genetic studies in women of Hispanic/Latina origin identified single nucleotide polymorphisms (SNPs) in the 6q25 region that correlate with Indigenous American ancestry and are protective against breast cancer. The underrepresentation of Latin American populations in public databases has hindered the study of the mechanisms by which these SNPs confer a protective effect in Latin American populations. We aimed to identify Indigenous American germline variants associated with breast cancer risk and to test their association with tumor gene expression in this region.

Breast cancer patients, part of the PEGEN-BC Study (N=1755), were included as cases and women from a pregnancy outcomes study in Peru as controls (N=3334). Genome-wide genotype data were available and missing genotypes were imputed using the TOPMED Imputation Server. Continental genetic ancestry was estimated sing ADMIXTURE with K=4. Logistic regression was used to test the association between each SNP in 6q25 and breast cancer risk adjusting by the first 10 principal components. Fine-mapping was performed using the FINEMAP tool to identify additional potential causal variants. We exome-sequenced 290 breast tumors of PEGEN-BC patients. Tumor subtype was assigned by the pam50 method. We excluded patients diagnosed with stage IV disease and with tumors classified as normal-like or as uncertain. Identification of cis-eQTLs was performed using the matrixeQTL R package, adjusting by age at diagnosis and Indigenous American ancestry. Colocalization analysis was performed by integrating the summary statistics of fine-mapping and eQTL analyses using the eCAVIAR tool.

Fine-mapping analysis revealed three potential independent variants associated with breast cancer risk that are located in or near regulatory regions: rs140068132 (odds ratio (OR)=0.53, p=2.2e-26), rs41289379 (OR=0.71, p= 2.8e-08), and rs7749659 (OR=1.3, p= 2.8e-08). Analyses stratified by subtype showed additional subtype-specific risk variants. Colocalization analysis identified breast cancer-associated variants in 6q25 that act as cis-eQTLs in a tumor-specific way and that regulate five different genes in the region. Among these genes, MTHFD1L, RMND1 and ZBTB2 haven been shown to be prognostic for different types of cancer. In conclusion, our results show an association between breast cancer risk genetic variants and gene expression in breast tissue.

2. HEALTH EQUITY IMPACT OF A TOBACCO TREATMENT PROGRAM AMONG PATIENTS WITH OR WITHOUT A UCD PRIMARY CARE PROVIDER AT UC DAVIS COMPREHENSIVE CANCER CENTER, 2017-2021

Nan Wang, MS, UC Davis, Department of Public Health Sciences; Susan Stewart, PhD, UC Davis, Department of Public Health Sciences; Elisa Tong, MD, UC Davis, Department of Internal Medicine

Introduction: Tobacco use after a cancer diagnosis can negatively impact treatment outcomes and the National Cancer Institute has funded cancer centers to implement tobacco treatment programs (TTP). This study aimed to assess whether the TTP at UC Davis (UCD) Comprehensive Cancer Center improved equity of smoking cessation assistance for patients with or without a UCD primary care provider (PCPs).

Methods: A repeated cross-sectional sample using Electronic Health Record (EHR) data was collected every six months from January 2017 to December 2021 (N=83,604). Current smokers aged >=18 were included in this study (N=4,718). The TTP implementation included provider outreach (starting 2018), referral by medical assistants and staff (2019), care gap outreach (2020), and a streamlined referral order (2021). Assistance was defined as medication or counseling orders. To examine whether the association between PCPs and assistance differs over time, a logistic regression model with an interaction term between PCPs and study year on assistance was estimated using generalized estimating equations (GEE) to account for within-patient correlation. We estimated the odds ratios for receiving assistance among patients with a UCD PCP vs. without a UCD PCP by year using a Bonferroni-Holm adjustment for multiple testing.

Results: Overall 38.2% of patients who smoke had UCD PCPs. Other characteristics included 51.2% females, 66.7% Whites, 38.9% were aged 65+ years old, 47.7% were covered by Medicare, 76.2% lived in metro areas, and 56.9% were last seen in medical oncology. The proportion of patients who smoke receiving cessation assistance significantly increased from 17.0% in 2017 (before the TTP began) to 41.0% in 2021 (P<.001). In 2017, those with a UCD PCP were twice as likely to receive assistance than those without a UCD PCP (22.5% vs. 11.8%; odds ratio [OR]: 2.08; 95% CI: 1.24-3.50). By 2021, this disparity in receiving assistance between patients with and those without a UCD PCP was considerably reduced (44.7% vs. 39.0%; OR: 1.13; 95% CI: 0.82, 1.56).

Conclusion: Overall, the TTP more than doubled the cessation assistance to patients who smoke. The program impact was even greater for patients without a UCD PCP by tripling cessation assistance and improving equitable assistance.

3. OPTIMIZATION OF TOTAL-BODY PET IMAGING OF BONE MARROW USING DUAL-ENERGY CT

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Purpose/Background: Bone marrow (BM) quantification with 18F-FDG PET is of broad clinical significance for detecting BM involvement in cancer staging and early prediction of response to immunotherapy. However, current BM quantification may be inaccurate because a unit volume of bone marrow may also consist of a fraction of spongy bone in which FDG activity is negligible, resulting in a potential underestimation of true BM uptake. Here we demonstrate this bone-led tissue fraction effect using dual-energy (DE) CT material decomposition and its impact on BM quantification with total-body PET.

Methods: Five cancer patients were scanned on the uEXPLORER total-body PET/CT scanner, and each dynamic data was acquired for 60 minutes. Prior Ethics Committee/IRB approval and informed consent were obtained. A DECT scan was performed with 80 kVp and 140 kVp to decompose each voxel into air, soft tissue and bone components. Kinetic modeling using a two-tissue compartmental model was performed for 40 ROI quantification with the ascending aorta as image-derived input function. A bone marrow volume is modeled as a mix of BM, cortical bone and blood. The measured 18F-FDG activity is a weighted sum of the three compositions. FDG uptake in cortical bone is negligible. The bone volume fraction (V_bone) from DECT was fixed in the kinetic model estimation.

Results: The estimated bone volume fraction was 0.211±0.053. With bone fraction correction (BFC), the standard uptake value (SUV) was 1.576±0.275 compared to 1.244±0.215 without BFC. The FDG net influx rate Ki and delivery rate K1 with BFC achieved 0.0068±0.001 and 0.228±0.125 compared to 0.0054±0.0009 and 0.181±0.106 without BFC. The increase in SUV was 26.6%±4.0% with BFC and its effect on SUV was statistically significant by the paired t test. Similarly, the gain of Ki and K1 using BFC achieved 26%±4.1% and the changes in them were also statistically significant.

Conclusion: Our study using DECT suggests current FDG SUV and kinetic quantification of BM are very likely underestimated in PET due to the significant bone volume fraction. A future work is to investigate the impact of this correction for evaluation of BM quantification in blood cancer staging.

4. TRANSCRIPTOME-WIDE STUDY OF TUMOR SAMPLES FROM PERUVIAN WOMEN IDENTIFIES DYSREGULATED PATHWAYS IN LUMINAL TUMORS TYPICALLY ASSOCIATED WITH MORE AGGRESSIVE DISEASE

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Purpose: Breast cancer incidence and outcomes vary by race/ethnicity in the US, but genetic studies have mainly focused on European populations. This lack of diversity can widen health disparities, particularly for Hispanic/Latinos. We aim to study relevant pathways in breast cancer subtype differentiation in patients from Peru to address this gap in knowledge.

Patients and Methods: Formalin fixed paraffin embedded tumor tissues samples were whole exome sequenced for a total of 292 patients, recruited by the Peruvian Breast Cancer Genomics Study (PEGEN-BC) from the Instituto Nacional de Enfermedades Neoplásicas (INEN) in Lima, Peru. Quality control was conducted and intrinsic tumor subtypes were classified using the adjusted PAM50 method. Differential gene expression between subtypes was performed and statistical significance was determined using FDR<0.05 for samples with at least log2 1.5-fold change. Pathway analyses were performed to explore differences among the subtypes using GSEA. Ancestral proportions for participants were estimated using germline genome-wide genotypes and the program Admixture.

Results: The mean age of patients was 50 and the median Indigenous American ancestry was 79%. PAM50 classification of the sequenced samples defined 20.2% of tumors as LumA, 27.9% as LumB, 27.1% as HER2, 22.5% as Basal and 2.3% as Normal. Transcriptomic pathway analysis showed that most of the significantly changed pathways were similar to those previously described such as upregulation of high proliferation pathways in LumB, HER2E and Basal tumors, and a strong dependency on the estrogen pathway for LumA. Top 20 significantly changed pathways show some unique findings: the eukaryotic translation initiation, eukaryotic translation elongation and ribosome pathways are upregulated in Basal and LumB, comparing to HER2 tumors, which is unexpected for LumB subtype given that these pathways are associated with uncontrolled proliferation of cancer cells and poor outcomes.

Conclusions: We identified novel pathways associated with breast cancer subtypes in individuals with high Indigenous American ancestry from Peru and are working on testing the robustness of these findings. If our findings are confirmed, results would suggest a more aggressive profile of Luminal subtypes in the studied samples from Peru, with implications for treatment and survival.

5. THE NOVEL SMALL MOLECULE INHIBITOR LLS132 REDUCES PANCREATIC CANCER GROWTH, IN PART, BY BLOCKING CELL CYCLE PROGRESSION

Laura Musumeci, PhD, UC Davis; Irena Krga, PhD, UC Davis; Kit S. Lam, MD, PhD, UC Davis School of Medicine; Ruiwu Liu, PhD, UC Davis School of Medicine, Gerardo G. Mackenzie, PhD, UC Davis

Pancreatic cancer, a leading cause of cancer mortality in the US with a five-year survival of around 11%, is one of the most lethal cancers. Surgery, which offers the only realistic hope, has a limited role, with only about 20% of patients undergoing resection of any variety. Current chemotherapy or radiation therapy regimens offer minimal or no help. Thus, there is a dire need for new agents against pancreatic cancer. Recently, we designed and synthesized multiple promising small molecule inhibitors with strong in vivo anticancer efficacy. Our novel lead agent LLS132 showed high potency in reducing pancreatic cancer cell growth and significantly reducing in vivo growth of these tumors. LLS132 (30 mg/kg; i.p 5x/week) reduced pancreatic tumor growth by 78%, compared to controls, and this effect was superior to that of gemcitabine (100 mg/kg; i.p 2x/week), which reduced tumor growth by only 48%. Of note, LLS132 was safe with mice showing no liver toxicity or changes in body weight. In addition, using a RNA-seq analysis of human pancreatic cancer Panc-1 cells treated with LLS132, we identified ribosomal biogenesis, and cell cycle DNA replication as key biological

processes affected by LLS132. We validated these findings by immunoblot. LLS132 blocked the cell cycle progression at S phase in human pancreatic cancer Panc-1 and Mia Paca-2 cells, while inducing little or no apoptosis. LLS132 also modulated the expression of proteins involved in S phase including MCM-7, Cyclin A2, CDK2 and p-ERK, hence suggesting a potential mechanism underlying its antiproliferative effects. Of note, both p-ERK and CDK-2 protein levels were also modulated in the xenograft samples. Furthermore, LLS132 synergized with nab-paclitaxel in both Panc-1 and MIA PaCa-2 pancreatic cancer cell lines. These preliminary results strongly indicate that LLS132 is safe and effective in multiple preclinical models of PDA, and provides synergistic therapeutic effects with nab-paclitaxel therapy, warranting further evaluation.

6. NAPHTHALENE-DNA ADDUCTS PERSIST AFTER 24 HOURS IN C57BL/6 MOUSE AIRWAY EXPLANTS

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Humans are widely exposed to naphthalene, a combustion product and air pollutant ubiquitous in our environment. Once inhaled, naphthalene is bioactivated by enzymes in the body to form toxic metabolites known to harm lung epithelial cells. Chronic naphthalene exposure causes tumors in the respiratory epithelium of the mouse lung and rat nose. Recent prior data from our labs have shown naphthalene forms stable DNA adducts (a genotoxic mechanism) at lung tumor sites in B6C3F1 mice, but the persistence of these adducts is largely unknown. We hypothesized DNA adducts formed by naphthalene metabolites would persist and still be detectable hours after initial exposure. Lungs were collected from wild-type C57BL/6 mice to explore persistence of adducts and reconfirm adduct formation in another strain. The lungs were microdissected to extract the conducting airway. The conducting airway was incubated with 14C-labeled naphthalene (250 uM) or metabolite 14C-1,2-naphthoquinone (250 uM) for 1 hour (T1), then processed immediately or allowed to incubate in unlabeled media for the remaining 23 hours (T24). DNA was extracted from the airway samples, processed into graphene, analyzed via accelerator mass spectrometry to measure isotope ratios, and then converted into measurements of chemically-induced DNA adducts. Two-way analysis of variance (ANOVA) with Tukey's post-hoc test showed there were significantly more naphthalene-DNA adducts and 1,2-naphthoquinone-DNA adducts versus unexposed controls ($P < 0.01$), as expected. There was no significant difference in the amounts of DNA adducts detected at T1 and T24. Cultures exposed to 1,2-naphthoquinone formed significantly more DNA adducts compared to those formed after exposure to naphthalene, regardless of exposure culture duration ($P<0.001$). No sex differences in the formation of DNA adducts were observed. Future experiments will investigate DNA adduct formation and stability in lung and liver after in vivo exposure to 14C-naphthalene. In conclusion, naphthalene- and 1,2-naphthoquinone-DNA adducts remain stable over 24 hours in wild-type C57BL/6 mouse airway explants, confirming adduct stability in another strain of mice and supporting a possible genotoxic mode of action for naphthalene carcinogenesis. Supported by T32 ES007058 & R01 ES020867.

Poster Presentation Abstracts

1. IFLIM: OPTICAL BIOPSY FOR COLORECTAL CANCER

Alba Alfonso Garcia, PhD, UC Davis Biomedical Engineering; Lisanne Kraft, MS, UC Davis Biomedical Engineering; Xiangnan Zhou, PhD, UC Davis Biomedical Engineering; Julien Bec, PhD, UC Davis Biomedical Engineering; Laura Marcu, PhD, UC Davis Biomedical Engineering; Dongguang Wei, MD, PhD, UC Davis Health; Dorina Gui, MD, PhD, UC Davis Health; Manan Jhaveri, MD, UC Davis Health; Shiro Urayama, MD, UC Davis Health; Asha Cogdill, MD, UC Davis Health

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, diagnosis, and intervention 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 and tumor display distinct fluorescence properties (i.e., intensity and lifetime) due to differences in metabolism and structure. Such contrast could be potentially resolved with intraoperative fluorescence lifetime imaging (iFLIm). This approach measures the fluorescence temporal dynamics, which is sensitive to the tissue microenvironment.

The iFLIm device was integrated with commercially available colonoscopes, enabling free-hand point measurements of the colonic mucosa from the cecum to the rectum. Tissue autofluorescence was induced by a 355 nm pulsed laser (0.25 uJ pulse energy, 0.6 ns pulse width, 460 HZ repetition rate), and detected in three spectral bands (390/40 nm, 470/28 nm, and 540/50 nm) that capture the fluorescence from the main tissue fluorophores, including structural proteins collagen and elastin, and cellular metabolic cofactors NADH and flavins. In vivo intraluminal imaging on 9 patients was performed before tissue collection as part of the patient's standard care. The resected specimen was diagnosed via standard histopathological evaluation. The study was approved by the University of California, Davis Institutional Review Board (IRB), and all patients provided informed consent before participation.

Current results show iFLIm contrast between polyps with high-grade dysplasia and adjacent tissue, with malignant tissue displaying shorter lifetime values and a spectral redshift. The fluorescence lifetime signatures differed between polyp types, which may enable in vivo polyp identification. Normal-appearing mucosa from different areas across the colon displayed different spectral lifetime signatures, with the sigmoid colon showing the most consistent values across patients. The location of the polyp within the colon may have a compounding effect that needs to be further examined.

These initial results support systematic studies in a larger patient cohort. Future work will focus on developing algorithms for the rapid identification of foci of malignancy and polyp types. iFLIm shows potential as an optical biopsy method for colorectal screening.

2. RESIDENTIAL PERCEPTIONS OF RISK IN AN AGRICULTURALLY-STRUCTURED COMMUNITY: A QUALITATIVE ASSESSMENT

Alfonso A. Aranda, University of San Francisco (UC Davis alumni)

This qualitative study utilized a community-based participatory research approach to investigate residential perceptions of risk in a farmworker community near Sacramento and the University of California, Davis. The aim was to explore how community members understand and experience exposure to environmental health hazards and how these perceptions impact community health practices. Participant-led focus groups (n=5) were conducted among English- and Spanish-speaking residents in Fall 2018. Participants were asked about their perceptions of environmental health risks, including pesticide exposure, air and water pollution, and access to healthcare. The study found that, contrary to research in other marginalized and resource-dependent communities, participants possess working knowledge and acute perceptions of risk specifically about exposure to carcinogenic pesticides in the local well water system. Our findings provide important insights into the experiences and perspectives of farmworkers regarding agricultural health hazards and their potential impact on cancer risk. The participatory approach underscores the importance of including community members in research and policy development, highlighting the need for increased attention to cancer prevention and environmental public health, particularly for vulnerable populations like farmworkers. Further research is needed to expand upon these findings and to inform interventions to address environmental health disparities in this population. Overall, this study contributes to the growing body of literature on the social determinants of health and underscores the importance of understanding the lived experiences of communities impacted by environmental health risks.

3. **ASSOCIATION BETWEEN BREAST CANCER SCREENING COMPLIANCE AND FOOD INSECURITY IN WOMEN WITH LOW INCOME FROM CALIFORNIA**

Charlotte L. Bergheimer, MS, UC Davis School of Medicine, Tamara Solorzano, MPH, UC Davis School of Medicine, Laura Fejerman, PhD, MSc, UC Davis Health Comprehensive Cancer Center

Background: Food insecurity has been associated with delayed breast cancer screening among low-income individuals and communities in the US. However, it is unclear if this association is due to poverty and related factors more generally (e.g., education, access to health care) or food insecurity specifically. Hence, we tested the association of food insecurity with being up-to-date with breast cancer screening recommendations in women with low-income from California.

Methods: Individual-level information on breast cancer screening and food security status from females ages 40-74 years with an annual household income below 200% of the federal poverty level was obtained from 2015-2016 California Health Interview Survey publicly available data. Bivariate and multivariate weighted logistic regression models were employed to test the association between breast cancer screening adherence and food insecurity, factoring in sociodemographic covariates including age, race/ethnicity, English proficiency, poverty level (dichotomized as 0-99% vs. 100-199% FPL), education, marital status, health insurance status, working status, and rurality.

Results: Among women with low-income from California with food insecurity, 70% were up to date with mammography screening, compared to 75% among those who had food security . Multivariable models will determine if this observed difference might be explained by the correlation between food insecurity and other important factors known to be associated with screening behavior, such as race/ethnicity, health insurance, working status, and rurality.

Conclusions: Food insecurity was inversely associated with being up-to-date with breast cancer screening. There is an imperative need to address breast cancer screening among low-income women in California, especially those who experience food insecurity.

Impact: Future studies should combine FI and breast cancer screening interventions to improve screening rates.

4. **DEVELOPMENT OF A PROMOTORES-BASED CERVICAL CANCER PREVENTION EDUCATION CURRICULUM FOR HISPANIC/LATINX WOMEN**

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Introduction: In the United States, Hispanic/Latinx (H/L) women face the highest cervical cancer incidence and mortality rates over all individuals in other racial/ethnic categories. While there is a general decreasing trend of cervical cancer rates in the country given the availability of preventive measures like Pap tests and HPV vaccines, research suggests that H/L women continue to face high incidence and mortality due to underutilization of these measures. Underutilization could be due to low health literacy among H/L women and a lack of culturally competent educational materials about cervical cancer prevention. To address this disparity, we are developing a program named “Mas Vale Prevenir”, to train Spanish-speaking community health educators (a.k.a. promotores) on cervical cancer prevention using tailored health education materials that are culturally relevant and align with the needs of the H/L community. The promotores model has demonstrated effectiveness in providing culturally and linguistically appropriate health education by building trusting relationships with the community.

Methods: To develop programmatic educational materials, we are applying a continuous stakeholder engagement approach. The program idea originated from conversations with members of H/L communities in California. A review of previously published educational materials was conducted to create the base content for an informational booklet for promotores. Three focus group sessions with promotores were held via Zoom to gather iterative feedback on different booklet versions. The Zoom session transcripts were analyzed through thematic content analysis to better understand what the promotores liked about the educational material that was developed for the program and what could be improved.

Results: Themes that came up during the focus groups included learning preferences, such as the use of graphics to complement text in the material, and opinions related to the content of the materials, such as its comprehensibility (e.g., simple but complete explanations) and cultural appropriateness.

Conclusion: Focus group feedback from the promotores is a useful tool in the development of cervical cancer prevention educational materials. As the promotores themselves are part of the H/L community, their perspective and insight ensures that “Mas Vale Prevenir” program material is culturally appropriate and relatable to other women in their communities.

5. IDENTIFYING FORCE-DEPENDENT PROTEIN INTERACTIONS SURROUNDING ACTIN FILAMENTS

Agustina Diener, Biomedical Engineering, Hikaru Katani, Biomedical Engineering, Yurina Araki, Biomedical Engineering, Volkmar Heinrich, Biomedical Engineering, Soichiro Yamada, Biomedical Engineering

Mechano-transduction is the process by which a cell senses, integrates, and converts mechanical stimuli into biochemical signals. This results in intracellular changes that regulate cell adhesion and cell behavior including cancer progression. Despite having a critical purpose in cell fate, the molecular details of this process are not well understood. Actin filaments are thought to be force-sensing, but the comprehensive list of proteins and signal cascades 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 Ftractin, an actin filament binding sequence. Using purified biotinylated samples from control and stretched cells, our preliminary mass spectrometry analysis of TurboID-Ftractin identified over 1000 proteins and we ranked them based on relative abundance of proteins in control and stretch samples. PLEK2 was one of the top candidates, however, the Western Blot and live cell stretch experiment could not confirm stretch dependent interactions. Further analysis identified three additional candidates: ARL15, B9D9, and PEX5. PEX5 was only present in the stretch sample based on the Western Blot, consistent with mass spectroscopy analysis. Based on a live cell stretch experiment, PEX5 colocalizes to fibrous structures upon cell stretch, thus demonstrating the feasibility of detecting force induced protein interactions. By identifying more proteins that interact with actin filaments under force-bearing conditions, we will better understand the molecular basis of mechano-transduction, which may uncover the potential role of this process in cancer.

6. DECIPHERING FORCE-INDUCED INTERACTIONS SURROUNDING KERATIN USING IN VITRO MICRONEEDLE STRETCH

Dah Som Kim, MS, UC Davis Biomedical Engineering, Tzu-Wei Gabriella Lai, BS, UC Davis Biomedical Engineering, Yuh-Ru Julie Lee, PhD, UC Davis Biology, Volkmar Heinrich, PhD, UC Davis Biomedical Engineering, Su Hao Lo, PhD, UC Davis School of Medicine, Soichiro Yamada, PhD, UC Davis Biomedical Engineering

Epithelial tissues serve as an important protective structure and account for greater than 80 percent of all human cancer cases. The keratin network provides mechanical integrity of epithelial tissues and may also serve as the force-sensing element in normal and cancer cells. Interestingly, cten, a protein known to act as both tumor suppressor and promoter, accumulates along force-bearing keratin fibers in vivo. Yet, the precise molecular interaction between keratin and cten remains unclear. To understand the mechano-biology of keratin and its implication in cancer, our goal is to define the force-induced protein-protein interactions surrounding the keratin network in vitro. The recombinant keratin 8 and keratin 18 were assembled into filaments and these filaments were stretched using a microneedle. When GFP proteins were added to the stretched keratin filaments, GFP binding to the keratin filaments was minimal. On the other hand, cten accumulated more intensely along stretched keratin filaments, suggesting that there is a force-induced interaction between cten and keratin filaments and that keratin filaments may be force-sensors of the cell. Currently, we are improving purification and assembly of keratin filaments to optimize them for microneedle stretching, as well as testing other proteins that may interact with the keratin network in a force-dependent manner. Since cten is known to participate in tumor development, the interaction between the keratin network and cten in response to mechanical force may provide novel insights into their roles in cancer progression.

7. MENTAL HEALTH AMONG CANCER SURVIVORS AND ADULTS WITHOUT A HISTORY OF CANCER IN THE UNITED STATES PRIOR TO AND DURING EARLY SARS/COVID-19 PANDEMIC

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Background: Poor mental health has been found to be more common among cancer survivors compared to those without a history of cancer, the impact of COVID-19 on mental health has not been examined among those with and without cancer using the same study population.
Objectives: We aimed to assess the association of sociodemographic factors, health status characteristics, and patient-provider communication practices with poor mental health among those with and without cancer during COVID compared to pre-COVID.

Methods: Nationally representative cross-sectional data (Health Information National Trends Survey, HINTS 5 2017-2020) was used for those with cancer (n=2,579) and without cancer (n=13,292) in pre-COVID (2017-2019) and COVID (2020). We calculated the prevalence of poor mental health through weighted descriptive analyses and evaluated differences between those with and without cancer by time using Differences-In-Differences (D-I-D). To obtain odds ratios (ORs) and 95% confidence intervals (95% CIs) of online patient-provider communications (OPPC), sociodemographic and health status characteristics with poor mental health, we developed multivariable weighted logistic regression models.

Results: The prevalence of poor mental health increased during COVID, yet was similar in with (41.9%) and without cancer (40.2%). Changes in poor mental health prior to and during COVID among those with cancer compared to those without were not significantly different. In multivariable models, individuals who had OPPC use (OR=1.39 95% CI 1.20-1.60 email/internet/tablet/smartphone), were young (ORs=1.98-3.25 18-64 years vs. ≥75 years), were females (OR=1.59, 1.39-1.80), were non-Hispanic Whites (vs. Hispanics, non-Hispanic Black/African Americans and Asians), were least educated (vs. college graduate OR=0.72, 0.56-0.94), had lowest income (vs. ≥$20,000 ORs=0.37-0.63), and had poor general health (vs. excellent health OR=0.31, 0.26-0.37) were more likely to have poor mental health. History of cancer and the early COVID pandemic were not associated with poor mental health.

Conclusions: The prevalence of poor mental health was high during the early COVID pandemic. We identified subgroups of adults with poor mental health, including those with OPPC use, with low socioeconomic status or who were younger. Our findings highlight the importance of targeted approaches for these vulnerable subgroups, such as through partnering with communities or local governments, involving related stakeholders, or applying life skills training.

8. IGFBP3 PROMOTES RESISTANCE TO OLAPARIB VIA MODULATING EGFR SIGNALING IN ADVANCED PROSTATE CANCER

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Castration-resistant prostate cancer (CRPC) is an incurable disease and a leading cause of cancer death in men worldwide. Olaparib (Lynparza) was among the first PARP inhibitor's (PARPi) approved for the treatment of CRPC tumors harboring DNA repair defects. However, clinical resistance to PARPi's has been documented. The mechanisms underlying resistance to PARPi's remain elusive. To study acquired resistance, we developed olaparib-resistant LN-OlapR and 2B-OlapR cell lines through chronic olaparib treatment of the olaparib-sensitive cell lines LNCaP and C4-2B, respectively. RNA-seq revealed IGFBP3 is overexpressed in both OlapR cell lines. IGFBP3 overexpression is correlated with poor clinical outcome and is thought to participate in DNA repair pathways. IGFBP3 plays a key role in the nonhomologous end joining (NHEJ) repair through a ternary complex with the epidermal growth factor receptor (EGFR) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). The IGFBP3/EGFR signaling axis is thought to modulate NHEJ repair and could have implications for PARPi sensitivity. Our data suggest that IGFBP3 expression promotes PARPi resistance by enhancing DNA repair capacity. We verified increased levels of IGFBP3 RNA and protein in both OlapR models. We found that RNAi inhibition of IGFBP3 decreases cell proliferation and increases γH2AX and cleaved-PARP protein levels in the resistant models, which suggests accumulation of DNA double strand breaks (DSBs) leading to genomic instability and cell death. We discovered increased phosphorylation of EGFR and DNA-PKcs in the resistant cells. Furthermore, silencing/inhibiting IGFBP3 and EGFR reduces OlapR cell viability and resensitizes resistant cells to treatment. Our findings demonstrated that inhibiting IGFBP3 and EGFR aids in PARPi sensitivity in the resistant setting. Future work will utilize OlapR models to study how the IGFBP3/EGFR/DNA-PKcs protein complex promotes the development of resistance. Understanding the role of IGFBP3 in PARPi resistance will enhance our ability to re-sensitize resistant CRPC to PARPi therapeutics.

9. **A NOVEL BI-SPECIFIC T CELL ENGAGER (BITE) TARGETING CD22 AND CD3 HAS BOTH IN VITRO AND IN VIVO ACTIVITY AND SYNERGIZES WITH BLINATUMOMAB IN AN ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TUMOR MODEL**

Daniel Levis, Joshua Meckler PhD, Daniel Vang, Joseph Tuscano MD

Immunotherapy has revolutionized cancer therapy. Two recently FDA-approved immunotherapies for B-cell malignancies target CD19, in the form of a Bispecific T-Cell Engager (BiTE) antibody construct or chimeric antigen receptor T (CAR-T) cells. Blinatumomab, an FDA-approved BiTE, binds to CD19 on B cells and to CD3 on T cells, mediating effector-target cell contact and T-cell activation that results in effective elimination of target B cells. Although CD19 is expressed by essentially all B-cell malignancies at clinical presentation, relapses with loss or reduction of CD19 surface expression are increasingly recognized as a cause of treatment failure. Therefore, there is a clear need to develop therapeutics for alternate targets. We have developed a novel BiTE consisting of humanized anti-CD22 and anti-CD3 single chain variable fragments. Target binding of the anti-CD22 and anti-CD3 moieties was confirmed by flow cytometry. CD22-BiTE promoted in vitro cell-mediated cytotoxicity in a dose and effector: target (E:T)-dependent fashion. Additionally, in an established acute lymphoblastic leukemia (ALL) xenograft mouse model, CD22-BiTE demonstrated tumor growth inhibition, comparable to blinatumomab. Further, the combination of blinatumomab and CD22-BiTE yielded increased efficacy in vivo when compared to the single agents. In conclusion, we report here the development of a new BiTE with cytotoxic activity against CD22+ cells which could represent an alternate or complementary therapeutic option for B-cell malignancies.

10. **ROLE OF DIETARY OMEGA-3 (N-3) FATTY ACIDS ON INTESTINAL BARRIER INTEGRITY IN MICE FED A HIGH-FAT DIET: IMPLICATION IN PANCREATIC CANCER DEVELOPMENT**

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Consumption of high-fat diets (HFD) are associated with intestinal barrier disruption, gut dysbiosis, and endotoxemia, all of which have been documented to accelerate pancreatic cancer development and progression. Omega-3 (n-3) polyunsaturated fatty acids (PUFAs) exert anti-inflammatory effects and have been shown to improve gut epithelial function and reduce intestinal permeability through tight junction (TJ)-regulated paracellular route. However, the potential impact of diets rich in fat and high in PUFAs on the modulation of intestinal permeability in the context of pancreatic carcinogenesis is unclear. Thus, we investigated the capacity of omega (n-3) fatty acid supplementation to mitigate HFD-induced intestinal permeability and endotoxemia in a mouse model of pancreatic cancer. Five weeks-old male and female KrasLSL-G12D; Ptf1aCre/+ (KC) mice were randomized to one of four diets: i) a control diet containing approximately 12% total calories from fat ii) the control diet supplemented with n-3 fatty acids, iii) an HFD containing approximately 60% total calories from fat (HF) or iv) the HFD supplemented with n-3 fatty acids. Consumption of a HFD for 7 weeks led to: i) an increase in the colon weight/length ratio, suggestive of inflammation; ii) increased plasma lipopolysaccharide (LPS) levels, iii) a decreased expression of tight junction (TJ) proteins (occludin and ZO-1) in the colon iii) increased colon levels of toll-like receptor 4 (TLR4), associated with increased exposure to LPS and inflammation. Supplementation with n-3 fatty acids reduced HFD-mediated TLR4 increased expression, and ameliorated the decreased expression of the TJ protein occludin. Moreover, supplementation with n-3 fatty acids also reduced plasma LPS levels, but this effect was only observed in female mice. Additional studies are currently underway to decipher the cellular mechanisms of this protective effect at the intestine level by diets high in n-3 fatty acids, and how these effects modulate pancreatic carcinogenesis.

11. **ADVANCING EVIDENCE OF THE ASSOCIATIONS BETWEEN SPECIFIC BENIGN BREAST DIAGNOSES AND FUTURE BREAST CANCER RISK**

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Benign breast disease (BBD) is a common breast biopsy finding encompassing a diverse spectrum of diagnoses. The risk of cancer associated with many specific BBD diagnoses and their joint associations with breast density have not been extensively studied. We estimate the future risk of invasive breast cancer associated with specific BBD diagnoses typically combined into two broad categories of non-proliferative lesions (NPL) and proliferative lesions without atypia (PWoA) and evaluate whether these associations differ by breast density or by the co-occurrence of pathologic descriptors. We included 711,802 women ages 35-79 years who underwent 2,606,759 mammograms in the Breast Cancer Surveillance Consortium from 1996-2017. We fit Cox proportional hazards models to estimate hazard ratios (HR)

associated with each combination of benign breast diagnoses, descriptors, and breast density. We used classification trees to group combinations of BBD diagnoses, breast density, age groups, and descriptors with similar magnitudes of associations with 5-year risk of invasive breast cancer. Compared with women without a prior breast biopsy, women with a PWoA BBD diagnosis and calcifications had a statistically significantly elevated risk for breast cancer in all breast density categories: almost entirely fatty HR = 2.18, 95% CI = 1.14 to 4.19, P=0.019; scattered fibroglandular densities HR = 1.74, 95% CI = 1.41 to 2.15, P<0.001; heterogeneously dense HR = 2.01, 95% CI = 1.72 to 2.35, P<0.001; extremely dense HR = 1.66, 95% CI = 1.17 to 2.36, P = 0.0042. Among women with dense breasts, the 0.1% of women with very high breast cancer risk (5-year risk>4%) were ≥60 years and had a PWoA BBD diagnoses of papilloma or radial scar. Women <60 years with fatty breasts were at low-average risk of breast cancer (0-1.66%) regardless of BBD diagnosis. Women ≥60 years with fatty breasts were at intermediate risk (1.67-2.49%) if they have certain NPL diagnoses such as fibroadenoma or adenosis. These findings provide strong support that specific BBD diagnoses in combination with breast density and presence of calcifications can more accurately identify groups of women at higher or lower risk of breast cancer than broad BBD categories.

12. EVALUATION OF METABOLITES DERIVED FROM PHENOLIC COMPOUNDS PRESENT IN OLEA EUROPAEA AND LIPPIA CITRIODORA IN PANCREATIC CANCER CELL LINES

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Phenolic compounds present in plants have been shown to have beneficial properties for the treatment of different chronic diseases, including cancer. However, it should be considered that the phenolic compounds are heavily metabolized by humans and, in most cases, the resulting metabolites are actually responsible for a large part of the observed effects, since they modulate multiple metabolic pathways and have mechanisms of action on gene expression. For that purpose, it is important to evaluate both the parent compounds, as well as their metabolites, since these are the compounds present in the blood circulation. We have previously identified some examples of metabolites that are present in the bloodstream of humans after ingestion of olive leaf (Olea europaea) and lemon verbena (Lippia citriodora) extracts. The major phenolic compounds present in each of the extracts, oleuropein in O. europaea and verbascoside in L. citriodora, are eventually fragmented and metabolized to give rise to various circulating metabolites. These include hydroxytyrosol, hydroxytyrosol glucuronide, dihydro-ferulic acid and its sulfate and glucuronides forms, as well as homovanillic acid and vanillic acid and their derived sulfate metabolites, respectively. Given the urgent need for new effective treatments for pancreatic cancer, we conducted a cytokinetic study to evaluate the anticancer effect of phenolic compounds present in olive leaf and lemon verbena and their respective metabolites in human pancreatic cancer cells (Panc-1 and MIA PaCa-2 cells). When comparing the parent compound to the metabolites present in olive leafs and lemon verbena, we observed that the most potent compounds reducing cancer cell growth were the dihydro-ferulic acid and vanillic acid sulfate, followed by homovanillic acid sulfate. This was consistently observed in both cell lines. In addition, vanillic acid sulfate and homovanillic acid sulfate induced cell death by apoptosis compared to their non-sulfate forms. Furthermore, vanillic acid sulfate reduced the levels of PARP, BclxL and cyclin E compared to vehicle control in Panc-1 cells. In conclusions, these preliminary studies suggest that the vanillic acid sulfate, a metabolite derived from vanillic acid, merits further evaluation for its anticancer effects.

13. DNA METHYLATION-MEDIATED SILENCING OF PDZRN3 PROMOTES METASTASIS IN PANCREATIC DUCTAL ADENOCARCINOMA

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Pancreatic ductal adenocarcinoma (PDA) is the third leading cause of cancer related deaths in the United States largely because most patients are diagnosed after the cancer has metastasized. No recurrent genetic mutation driving PDA metastasis has been found, suggesting that PDA metastasis is instead driven by epigenetic factors, such as DNA methylation. At promoters, methylation is commonly associated with gene silencing and aberrant, genome-wide methylation is a characteristic of many cancers, including PDA. However, the specific genes whose aberrant DNA methylation promote PDA metastasis are unknown. We identified PDZRN3 promoter methylation as a contributor of PDA metastasis. PDZRN3 is a ubiquitin ligase implicated in regulation of the non-canonical Wnt/planar cell polarity (PCP) pathway, which has been shown in several cancers to promote metastasis via cytoskeletal rearrangements. We found that the PDZRN3 promoter is hypermethylated and associated with gene downregulation in metastatic compared to primary tumor mouse- and patient-derived organoids. This PDZRN3 downregulation is associated with worse survival

outcomes in PDA patients. Furthermore, knockdown of Pdzrn3 in mouse PDA cell lines resulted in increased migration rates and filopodia formation, indicating that Pdzrn3 silencing promotes metastatic character. Knockdown of Pdzrn3 also resulted in increased expression of Dvl3, a conductor of Wnt/PCP signaling. This is the first study of Wnt/PCP signaling and PDZRN3 in PDA metastasis. Our findings suggest that PDZRN3 hypermethylation status may be beneficial as a cell-free DNA biomarker for diagnosis of late-stage PDA and that Wnt/PCP components should be considered in targeted therapeutic strategies for treatment of late-stage PDA.

14. ENGRAILED-1 PROMOTES PANCREATIC CANCER METASTASIS

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Engrailed-1 (EN1) is a critical homeodomain transcription factor (TF) required for neuronal survival, and EN1 expression has been shown to promote aggressive forms of triple negative breast cancer. Here, we report that EN1 is aberrantly expressed in a subset of pancreatic ductal adenocarcinoma (PDA) patients with poor outcomes. EN1 predominantly repressed its target genes through direct binding to gene enhancers and promoters, implicating a role in the acquisition of mesenchymal cell properties. Gain- and loss-of-function experiments demonstrated that EN1 promoted PDA transformation and metastasis in vitro and in vivo. Our findings nominate the targeting of EN1 and downstream pathways in aggressive PDA.

15. FORCE-INDUCED ACCUMULATION OF TENSIN PROTEINS ALONG KERATIN FIBERS

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Transmission of mechanical force across cell adhesive contacts plays an important role in cell proliferation and differentiation, as well as in cancer progression. The tensin family are critical proteins at focal adhesions. We have shown that cten, the fourth member of the tensin family, is responsive to externally applied forces and accumulates along keratin fibers upon cell stretch. Recently, we discovered that tensin 3, the third member of the tensin family, also binds to keratin fibers upon cell stretch, but tensin 1 and 2 does not. While tensin 3 is thought to be a key part of cell migration and growth in cancer cells, the exact physiological role of this force-induced accumulation remains unclear. To understand the role of tensins in mechano-transduction, the first critical step is to define the amino acid sequence of tensin 3 required for its force-sensitivity. Interestingly, the removal of the C terminus SH2 and PTB domains enhanced tensin 3 recruitment to the force-bearing keratin fibers, suggesting that the C-terminus of tensin 3 plays a suppressive role in the force-induced recruitment of tensin 3. Based on 2D structure prediction software, tensin 3 is largely disordered, but contains unique alpha helical structures flanking the central region of tensin 3. Removal of one or two predicted helical sequences resulted in the reduction of force-sensitivity. In addition, isolating the helical structures by removing the sequences between them resulted in the highest force-induced recruitment. These results suggest that tensin 3's force-sensitivity is tightly regulated and distinct from cten. By resolving the molecular details of tensin 3's force-sensitivity, we may be able to unravel the force-dependent regulation of cancer progression.