

UC DAVIS
HEALTH

**COMPREHENSIVE
CANCER CENTER**

27th Annual Cancer Research Symposium
September 30 and October 1, 2021

<https://health.ucdavis.edu/cancer/research/education-training/symposia.html>



FROM THE DIRECTOR



I am pleased to welcome you to the UC Davis Comprehensive Cancer Center's 27th Annual Symposium. In its 27th year, the Annual Symposium event highlights cancer research efforts conducted by our Cancer Center members. Our long-standing symposium brings together the many talents and passions of investigators devoted to solving the problem of cancer across the entire spectrum from prevention to survivorship. This year's two-day virtual event will be organized into four main sessions and two poster sessions: Thursday, Session I – Population Sciences and Health Disparities, chaired by Dr. Shehnaz Hussain; Session II – Career Development and Education, chaired by Dr. Frederick Meyers; Session III – Basic/Translational Science, chaired by Dr. Luis Carvajal-Carmona; and Friday, Session IV – Clinical Research, chaired by Dr. Karen Kelly. Virtual poster sessions will allow cancer focused investigators to highlight their innovative science.

The keynote presentation in Session I, *Improving Effectiveness of Lifestyle Interventions*, brings renowned scientist Dr. Sarah-Jeanne Salvy.

Her research focuses on multisystemic interventions that can be widely disseminated and sustained, and on the influence of social factors on health.

Session II will feature a panel on *Diverse Scholars Finding Success at UC Davis* with speakers spanning the career continuum at UC Davis: Erin Doherty, PhD Candidate; Dr. Diedre Reitz, Postdoctoral Scholar; Dr. Nicole Coggins, Postdoctoral Scholar; Dr. Alan Lombard, Assistant Professional Researcher; and Dr. Luke Wittenburg, Associate Professor. These outstanding cancer investigators will share their experiences and provide insights for aspiring researchers.

The keynote lecture for Session III will be given by Dr. Ludmil Alexandrov from UC San Diego, whose research focuses on understanding mutational processes in cancer to improve treatment targeting and develop better prevention strategies. His presentation is entitled *The Repertoire of Mutational Signature in Human Cancer*.

Our final keynote and David R. Gandara Lectureship Awardee for Friday's Session IV will be given by Dr. Peter Nelson, a nationally recognized prostate researcher. He will speak on *Cancer Therapy Resistance: Mechanisms, Challenges and Opportunities*.

In addition to our keynote and panel speakers, we are also highlighting new cutting-edge cancer research from UC Davis. For twenty-seven years this event has allowed us to introduce new faculty, feature research by students, and promote programmatic and multidisciplinary interactions.

I am certain that you will find this event to be a remarkably productive experience. Our team looks forward to interacting with you and sharing new knowledge through this forum.

Thank you for your continued support.

Sincerely,

A handwritten signature in black ink that reads "Primo N. Lara, MD". The signature is written in a cursive style.

Primo N. Lara, MD
Director, UC Davis Comprehensive Cancer Center
Executive Associate Dean for Cancer Programs
Professor, Division of Hematology and Oncology, Department of Internal Medicine
Codman-Radke Endowed Chair for Cancer Research

SYMPOSIUM COMMITTEE MEMBERS

Primo N Lara, MD

Director, UC Davis Comprehensive Cancer Center

Executive Associate Dean for Cancer Programs

Professor, Division of Hematology and Oncology, Department of Internal Medicine

Division of Hematology-Oncology, Department of Internal Medicine

Codman-Radke Endowed Chair for Cancer Research

Shehnaz Hussain, PhD, ScM

Associate Director for Population Sciences, UC Davis Comprehensive Cancer Center

Professor, Department of Public Health Sciences

Frederick J Meyers, MD, MACP

Associate Director for Education, Training, and Career Development, UCD Comprehensive Cancer Center

Director, Center for Precision Medicine and Data Sciences

Professor, Division of Hematology and Oncology, Department of Internal Medicine

Luis Carvajal-Carmona, PhD

Associate Director for Basic Sciences, UCD Comprehensive Cancer Center

Founder and Director, Latinos United for Cancer Health Advancement (LUCHA) Initiative

Professor and Auburn Community Cancer Endowed Chair in Basic Science, Genome Center and Department of Biochemistry and Molecular Medicine

Karen Kelly, MD

Associate Director for Clinical Research, UCD Comprehensive Cancer Center

Professor, Division of Hematology and Oncology, Department of Internal Medicine

Jennifer Rene Harmon Tegley and Elizabeth Erica Harmon Endowed Chair in Cancer Clinical Research

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Administration

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Research Program
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Education Specialist

Connor Murphy
Student Assistant

Christian Joyce
Marketing Specialist

Chelsey Reeves
Executive Assistant

Peggy Martin
Executive Assistant

Rui Wu
Data System Analyst

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AGENDA

27th Annual Cancer Research Symposium

Thursday, September 30, 2021

SESSION I: Population Sciences and Health Disparities

Chair: Shehnaz Hussain, PhD, ScM

Time	Title	Presenter	Location
8:30 – 8:40 am	Introduction and Welcome	Primo Lara, MD Director, UC Davis Comprehensive Cancer Center	Zoom
8:40 – 9:10 am	Keynote Presentation: “Improving Effectiveness of Lifestyle Interventions”	Sarah-Jeanne Salvy, PhD Associate Professor, Department of Medicine, SOCCI Cancer Research Center for Health Equity, Adjunct Associate Professor, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Cedar-Sinai Medical Center	
9:10 – 9:25 am	Q&A		
9:25 – 9:40 am	“Significance of the Gut-Liver Axis for Progression Along the Disease Continuum from NAFLD to HCC”	Shehnaz Hussain, PhD Professor, Department of Public Health Sciences, Associate Director for Population Sciences, UC Davis Comprehensive Cancer Center	
9:40 – 9:45 am	Q&A		
9:45 – 10:00 am	“Comparative Metabolomics of Hispanic and Caucasian Non-Alcoholic Fatty Liver Disease: A Pilot Study”	John Newman, PhD Research Chemist, USDA ARS Western Human Nutrition Research Center, Associate Adjunct Professor, Department of Nutrition, UC Davis	
10:00 – 10:05 am	Q&A		
10:05 – 10:15 am	Break		
10:15 – 10:30 am	“Genetic Diversity, Diet and Susceptibility to Hepatic Steatosis in Mice”	Brian Bennett, PhD Research Leader, USDA ARS Western Human Nutrition Research Center, Associate Adjunct Professor, Department of Nutrition, UC Davis	
10:30 – 10:35 am	Q&A		
10:35 – 10:50 am	“Bile Acid Dysregulation and Cancer Risk”	Yu-Jui “Yvonne” Wan, PhD Professor and Vice Chair of Research, Department of Pathology and Laboratory Medicine, UC Davis	
10:50 – 10:55 am	Q&A		
10:55 – 11:10 am	“Hepatocyte p53 Ablation Induces Metabolic Dysregulation that is Corrected by Vertical Sleeve Gastrectomy in Mice”	Bethany Cummings, DVM, PhD Associate Professor, Department of Surgery, UC Davis	
11:10 – 11:15 am	Q&A		

SESSION II: Career Development and Education

Chair: Frederick Meyers, MD, MACP

Time	Title	Presenter	Location
11:15 – 12:00 pm	Panel: “Diverse Scholars Finding Success at UCDCCC”	<p>Erin Doherty, BS PhD Candidate, Department of Chemistry, UC Davis</p> <p>Luke A. Wittenburg DVM, PhD, DACVCP Associate Professor, Developmental Cancer Therapeutics, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, UC Davis</p> <p>Diedre Reitz, PhD Postdoctoral Fellow, Department of Microbiology and Molecular Genetics, UC Davis</p> <p>Alan Lombard, PhD Assistant Professional Researcher, Department of Urologic Surgery, UC Davis</p> <p>Nicole Coggins, PhD Postdoctoral Scholar, Genome Center and Department of Biochemistry and Molecular Medicine, UC Davis</p>	Zoom
12:00 – 1:30 pm	Poster Session		Zoom

SESSION III: Basic/Translational Science

Chair: Luis Carvajal-Carmona, PhD

Time	Title	Presenter	Location
1:30 – 2:00 pm	Keynote Presentation: “The Repertoire of Mutational Signature in Human Cancer”	Ludmil B. Alexandrov, PhD Assistant Professor of Cellular and Molecular Medicine and Bioengineering, UC San Diego	Zoom
2:00 – 2:15 pm	Q&A		
2:15 – 2:30 pm	“Therapeutic Targeting of Tumor Lineage Plasticity in Therapy-Resistant Prostate Cancer”	Hongwu Chen, PhD Professor, Department of Biochemistry and Molecular Medicine, UC Davis	
2:30 – 2:35 pm	Q&A		
2:35 – 2:50 pm	“Spatial RNA Profiling Reveals Cell Type-Specific Biomarker Expression During Melanoma Development.”	Maija Kiuru, MD, PhD Associate Professor of Clinical Dermatology and Pathology, Department of Dermatology, UC Davis	
2:50 – 2:55 pm	Q&A		
2:55 – 3:05 pm	Break		
3:05 – 3:20 pm	“Targeting Epigenetic Vulnerabilities in Breast Cancer”	Sanchita Bhatnagar, PhD Associate Professor, Department of Medical Microbiology and Immunology, UC Davis	
3:20 – 3:25 pm	Q&A		
3:25 – 3:40 pm	“Disrupting the Rbm38-eIF4E Complex to Increase p53 Expression as a Potential Cancer Therapeutic Strategy”	Christopher Lucchesi, PhD Postdoctoral Scholar, Department of Surgical & Radiological Sciences, UC Davis	
3:40 – 3:45 pm	Q&A		

End of Day 1

Friday, October 1, 2021

Time	Title	Presenter	Location
8:00 – 9:30 am	Poster Session		Zoom
SESSION IV: Clinical Research <i>Chair: Karen Kelly, MD</i>			
9:30 – 10:00 am	David R. Gandara Lectureship on Developmental Therapeutics: “Cancer Therapy Resistance: Mechanisms, Challenges and Opportunities”	Peter Nelson, MD Member, Divisions of Human Biology and Clinical Research, Fred Hutchinson Cancer Research Center, Professor, Division of Medical Oncology, University of Washington, Head, Program in Prostate Cancer Research PI, Pacific Northwest Prostate Cancer SPORE	Zoom
10:00 – 10:15 am	Q&A		
10:15 – 10:30 am	“Translation of Bladder Cancer Therapeutics”	Maria Mudryj, PhD Professor and Vice Chair of Education and Outreach, Department of Medical Microbiology and Immunology, UC Davis Mamta Parikh, MD, MS Assistant Professor, Division of Hematology and Oncology, UC Davis	
10:30 – 10:35 am	Q&A		
10:35 – 10:50 am	“Targeting the DNA-Binding Domain of the Androgen Receptor in Castration Resistant Prostate Cancer”	Paramita Ghosh, PhD Professor, Department of Biochemistry and Molecular Medicine, Department of Urologic Surgery, UC Davis Ruiwu Liu, PhD Research Scientist, Department of Biochemistry and Molecular Medicine, UC Davis	
10:50 – 10:55 am	Q&A		
10:55 – 11:05 am	Break		
11:05 – 11:20 am	“Characterization and Novel Targeting of the AKR1C3/AR/AR-V7 Axis for the Treatment of Lethal Prostate Cancer”	Chengfei Liu, MD, PhD Assistant Professor, Department of Urologic Surgery, UC Davis	
11:20 – 11:25 am	Q&A		
11:25 – 11:40 am	“A Phase 2 Neo-adjuvant Biomarker Driven Clinical Trial for High-Risk Prostrate Cancer”	Marc Dall’Era, MD Professor and Vice Chair, Department of Urologic Surgery, UC Davis	
11:40 – 11:45 am	Q&A		
11:45 – 11:55 am	Closing Remarks and Poster Awards Announcement	Primo Lara, MD Director, UC Davis Comprehensive Cancer Center	
Symposium Close			

ORAL PRESENTATIONS

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Abstracts of oral presentations (Friday): page 19-22

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

Sarah-Jeanne Salvy, PhD is faculty in the Cedars-Sinai Cancer Research Center for Health Equity. Dr. Salvy has been trained in Clinical Psychology and she has expertise in behavioral dietary and physical activity interventions across the life course. Her work focuses on multisystemic interventions that can be widely disseminated and sustained, and on the influence of social factors on health. She is currently MPI on two randomized clinical trials (R01HD092483-A1; U54MD000502) evaluating the implementation of these obesity prevention interventions in Southern California and in Central Alabama. Dr. Salvy is also MPI on a multi-site randomized control trial (RCT; NCI Provocative Question; 1 R01 CA258222-01) testing whether time-restricted eating (TRE) improves clinical outcomes among rectal cancer patients, and she is co-investigator on a DoD-funded RCT (DoDPR172125) testing the effectiveness of TRE in adults with type 2 diabetes. Dr. Salvy is also PI or site PI on trials evaluating the effectiveness of environmental and self-regulatory strategies to optimize weight management outcomes in adults and pediatric populations. This research seeks to address the pragmatic question of how to best optimize behavior change.



Sarah-Jeanne Salvy, PhD

Associate Professor, Department of Medicine, SOCCI Cancer Research Center for Health Equity, Adjunct Associate Professor, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Cedar-Sinai Medical Center



Ludmil B. Alexandrov, PhD

Assistant Professor of Cellular and Molecular Medicine and Bioengineering, UC San Diego

Ludmil Alexandrov, PhD is an Assistant Professor in the Department of Cellular and Molecular Medicine as well as the Department of Bioengineering at University of California San Diego. He earned his Bachelor of Science degree in Computer Science from Neumont University and received his Master's of Philosophy in Computational Biology as well as his Ph.D. in Cancer Genetics from the University of Cambridge.

Ludmil's research has been focused on understanding the mutational processes in cancer. In 2013, he developed the first comprehensive map of the mutational signatures in human cancer. More recently, Ludmil mapped the signatures of clock-like mutational processes operative in normal somatic cells, demonstrated that mutational signatures have the potential to be used for targeted cancer therapy, and identified the mutational signatures associated with tobacco smoking.

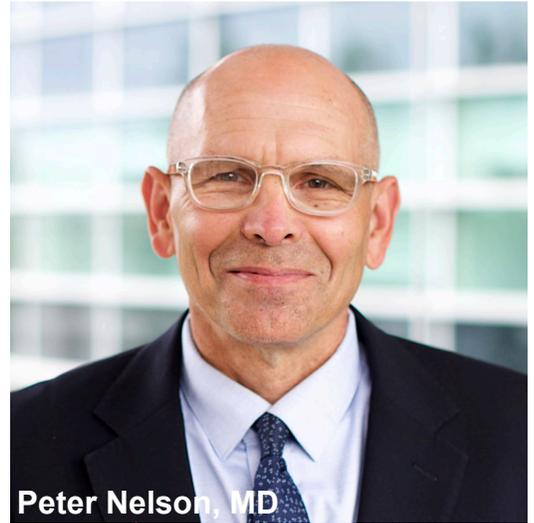
Ludmil has over 100 publications in peer-reviewed journals from which 22 publications in Nature, Science, or Cell and another 34 publications in Nature Genetics, Nature Medicine, Cancer Cell, Science Translational Medicine, PNAS, or Nature

Communications. In 2014, Ludmil Alexandrov was recognized by Forbes magazine as one of the "30 brightest stars under the age of 30". In 2015, he was awarded the Prize for Young Scientists in Genomics and Proteomics by Science magazine and SciLifeLab, and he also received a Harold M. Weintraub Award by the Fred Hutchinson Cancer Center. In 2016, Ludmil was awarded the Carcinogenesis Young Investigator Award by Oxford University Press. In 2018, Ludmil was awarded the Balfour Prize Lecture of the Genetics Society, an Alfred P. Sloan Research Fellowship in Computational & Evolutionary Molecular Biology, and an Early Career Award by The International Academy for Medical and Biological Engineering. In 2019, Ludmil was awarded a Packard Fellowship for Science and Engineering and was named as an Abeloff V Scholar. In 2020, Ludmil was awarded an Outstanding New Environmental Scientist (ONES) Award by National Institute of Environmental Health Sciences. Ludmil is currently one of six co-investigators leading the Mutographs of Cancer project, a \$25 million Cancer Grand Challenge initiative to identify the unknown cancer-causing factors.

Peter Nelson, MD is a Member of the Divisions of Human Biology and Clinical Research at the Fred Hutchinson Cancer Center and Professor of Medicine in the Division of Medical Oncology at the University of Washington.

He received an MD degree and completed residency training in internal medicine at the University of Kansas followed by a biotechnology fellowship at the NIH. He completed a medical oncology fellowship at the University of Washington with postdoctoral training under the mentorship of Leroy Hood.

Dr. Nelson's research has focused on developing a comprehensive understanding of the molecular alterations that drive the development and progression of prostate cancer. A component of this work involves developing strategies to overcome cancer therapy resistance.



Peter Nelson, MD

*Member, Divisions of Human Biology and Clinical Research, Fred Hutchinson Cancer Research Center, Professor, Division of Medical Oncology, University of Washington, Head, Program in Prostate Cancer Research
PI, Pacific Northwest Prostate Cancer SPORE*

ABSTRACTS OF ORAL PRESENTATIONS (THURSDAY)

SESSION I: Populations Sciences and Health Disparities

Chair: Shehnaz K Hussain, PhD, ScM

KEYNOTE LECTURE: IMPROVING EFFECTIVENESS OF LIFESTYLE INTERVENTIONS

Sarah-Jeanne Salvy, PhD, Associate Professor, Department of Medicine, SOCCI Cancer Research Center for Health Equity, Adjunct Associate Professor, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Cedar-Sinai Medical Center

Initiating and maintaining behavior change is ubiquitously difficult, and this is especially true for overburdened and under-resourced individuals. Dr. Salvy will be discussing challenges to traditional disease-preventing and health-promoting interventions and describe ongoing work focusing on increasing effectiveness of lifestyle interventions. Dr. Salvy will provide an overview of ongoing obesity, diabetes, and cancer trials spanning multisystemic interventions that can be widely disseminated and sustained. This work includes (1) the integration of obesity prevention within Maternal and Child Health Services in Southern California and Central Alabama; (2) the use of time-restricted eating (TRE) among patients with rectal cancer and type 2 diabetes; and (3) comparing environmental and self-regulatory strategies to optimize weight management outcomes in commercially available weight loss programs. This work seeks to address the pragmatic question of how to best optimize behavior change, while highlighting the importance of divergent thinking in creative science.

SIGNIFICANCE OF THE GUT-LIVER AXIS FOR PROGRESSION ALONG THE DISEASE CONTINUUM FROM NAFLD TO HCC

Shehnaz Hussain, PhD, Professor, Department of Public Health Sciences, Associate Director for Population Sciences, UC Davis Comprehensive Cancer Center

The liver and the gut coordinate and influence each other via tight bidirectional links through the biliary tract, portal vein, and systemic circulation. Several components of the gut-liver axis are relevant to HCC development including diet composition, bile acids, integrity of the intestinal barrier, microbiome diversity and composition, microbial antigens, and immune response mediators. Dr. Hussain will discuss recent findings from her ongoing molecular epidemiological studies based in prospective cohorts and case-control studies where she has focused on several of these risk factors and biomarkers. The underlying hypothesis of this research is that the liver is susceptible to immune-modulating and genotoxic effects of gut microbial components and products which occurs in the setting of dysbiosis and reach the liver when barrier function is compromised. Dr. Hussain will discuss the implications of these findings for cancer prevention through ongoing and planned chemoprevention studies.

COMPARATIVE METABOLOMICS OF HISPANIC AND CAUCASIAN NON-ALCOHOLIC FATTY LIVER DISEASE: A PILOT STUDY

John Newman, PhD, Research Chemist, USDA ARS Western Human Nutrition Research Center, Associate Adjunct Professor, Department of Nutrition, UC Davis

Nonalcoholic fatty liver disease (NAFLD) is a progressive condition that includes steatosis (NAFL) and nonalcoholic steatohepatitis (NASH). Hispanics (HIS) are afflicted with NAFLD at a higher rate and severity compared to other ethnicities. To date, the mechanisms underlying this disparity remain unelucidated. In this pilot study, we compared untargeted plasma metabolomic profiles for primary metabolism, complex lipids, choline and related compounds between a group of HIS (n =7) and White

Caucasian (CAU, n =8) subjects with obesity and biopsy-characterized NAFL to ethnicity-matched lean healthy controls (n =14 HIS and 8 CAU). We also compared liver and plasma profiles in a group of HIS and CAU subjects with obesity and NASH of comparable NAFLD Activity Scores, to BMI-matched NASH-free subjects in both ethnicities. NAFL was associated with elevated plasma lipids and acylcarnitines, in both ethnicities, but signs of metabolic dysregulations including elevated triglycerides, acylcarnitines and free fatty acids, were more pronounced in HIS, independent of obesity. With NASH progression, ethnicity-related differences in the hepatic profile, included higher free fatty acids and lysophospholipids seen in HIS, suggesting lipotoxicity involved in NASH progression. We also observed higher hepatic and plasma triglycerides, lower hepatic phospholipids with signs of impaired hepatic mitochondrial β -oxidation. Together, these findings provide preliminary evidence indicating ethnicity-related variations possibly modulating NAFLD risk and progression rate.

GENETIC DIVERSITY, DIET AND SUSCEPTIBILITY TO HEPATIC STEATOSIS IN MICE

Brian Bennett, PhD, Research Leader, USDA ARS Western Human Nutrition Research Center, Associate Adjunct Professor, Department of Nutrition, UC Davis

Mice have provided critical mechanistic understandings of clinical traits related to hepatic steatosis. We have investigated the diet- and strain-dependent effects on metabolic traits in the eight Collaborative Cross (CC) founder strains (A/J, C57BL/6J, 129S1/SvImJ, NOD/ShiLtJ, NZO/HILtJ, CAST/EiJ, PWK/PhJ, and WSB/EiJ) and an 8-way outbred cross of these strains. Using liver transcriptomics analysis, modules of transcripts associated with liver triglyceride content which have been identified to identify candidate genes and pathways associated with hepatic steatosis.

BILE ACID DYSREGULATION AND CANCER RISK

Yu-Jui "Yvonne" Wan, PhD, Professor and Vice Chair of Research, Department of Pathology and Laboratory Medicine, UC Davis

Introduction: Bile acids (BAs) are produced by hepatic and bacterial enzymes. They regulate metabolism and inflammatory response at the systemic level. Dysregulated BA synthesis or reduced expression of bile acid receptor farnesoid x receptor (FXR) is found in patients with metabolic diseases, autoimmune hepatitis, and liver cirrhosis as well as liver cancer. Our research goal is to understand the effect of diet through the gut microbiota and BAs on the development of non-alcoholic steatohepatitis (NASH), which can progress into liver cancer.

Methods and Results: Wild type (WT) and FXR knockout (KO) mice were given a control (CD) or Western diet (WD) for 10 months. Both WD intake and lack of FXR led to the development of NASH. WD-feeding of FXR KO mice had the most serious NASH in a male predominant manner. Depending on diet provided, broad-spectrum antibiotics eliminated most gut bacteria and affected hepatic inflammation differently in FXR KO mice. In CD-fed mice, a cocktail of ampicillin, neomycin, metronidazole, and vancomycin completely blocked hepatic inflammatory cell infiltration. However, this cocktail of antibiotics was not able to eliminate hepatic inflammation in WD-fed FXR KO mice. Bacterial sequencing data revealed that Proteobacteria and Bacteroidetes persisted after the broad-spectrum antibiotic treatment in the WD-fed FXR KO mice. In contrast, the Gram-negative coverage antibiotic polymyxin B increased Firmicutes, decreased Proteobacteria, and eliminated hepatic inflammation in WD-fed FXR KO male mice. These data suggest that the negative impacts of WD on the liver may be explained in part by the persistent presence of pro-inflammatory Proteobacteria as well as the reduction of anti-inflammatory Firmicutes in the gut.

WD-fed mice are obese and FXR KO mice are lean, but both have dysregulated BA synthesis and NASH with reduced colonic butyrate and fecal *bcoA*, a butyrate generating gene. The significance of fecal butyrate was further evaluated by fecal microbiota transplantation (FMT). The feces from 15-month-old WD-fed FXR KO mice, which lacked butyrate-generating bacteria, were orally transplanted to 7-month-old WD-fed FXR KO mice with or without butyrate supplementation. FMT of butyrate-

deficient feces increased hepatic lymphocyte infiltration, and butyrate supplementation reversed it. Summary: FXR KO, which has elevated BA pool size and dysregulated BA synthesis as well as dysbiosis, develops NASH. Altering the gut microbiota and BA profiles by antibiotic treatments, FMT, and dietary supplementation of butyrate affect hepatic inflammation and the development of NASH.

HEPATOCTYTE p53 ABLATION INDUCES METABOLIC DYSREGULATION THAT IS CORRECTED BY VERTICAL SLEEVE GASTRECTOMY IN MICE

Bethany Cummings, DVM, PhD, Associate Professor, Department of Surgery, UC Davis

p53 has been implicated in the pathogenesis of obesity and diabetes; however, the mechanisms and tissue sites of action are incompletely defined. Therefore, we investigated the role of hepatocyte p53 in metabolic homeostasis using a hepatocyte-specific p53 knockout mouse model. To gain further mechanistic insight, we studied mice under two complementary conditions of restricted weight gain: vertical sleeve gastrectomy (VSG) or food restriction. VSG or sham surgery was performed in high-fat diet-fed male hepatocyte-specific p53 wild-type and knockout littermates. Sham-operated mice were fed ad libitum or food restricted to match their body weight to VSG-operated mice. Hepatocyte-specific p53 ablation in sham-operated ad libitum-fed mice impaired glucose homeostasis, increased body weight, and decreased energy expenditure without changing food intake. The metabolic deficits induced by hepatocyte-specific p53 ablation were corrected, in part by food restriction, and completely by VSG. Unlike food restriction, VSG corrected the effect of hepatocyte p53 ablation to lower energy expenditure, resulting in a greater improvement in glucose homeostasis compared with food restricted mice. These data reveal an important new role for hepatocyte p53 in the regulation of energy expenditure and body weight and suggest that VSG can improve alterations in energetics associated with p53 dysregulation.

Session II: Cancer Career Development and Training

Chair: Frederick Meyers, MD, MACP

PANEL: DIVERSE SCHOLARS FINDING SUCCESS AT UCDCCC

Erin Doherty, BS, PhD Candidate, Department of Chemistry, UC Davis

Erin Doherty is a fifth year PhD Candidate in Chemistry with a Designated Emphasis in Biotechnology. She received her BS in Biochemistry from Cal Poly San Luis Obispo. At UC Davis she works in the lab of Dr. Peter Beal optimizing strategies for Site-Directed RNA Editing. She was previously supported by an NIH T32 Training Grant in Chemical Biology and is currently funded by an NIH F31 Ruth L. Kirschstein Predoctoral Individual National Research Service Award with the research proposal, "Site-directed RNA Editing to Modulate Kinase Activity as a Chemotherapeutic."



Luke A. Wittenburg DVM, PhD, DACVCP, Associate Professor, Developmental Cancer Therapeutics, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, UC Davis

Dr. Wittenburg obtained his undergraduate degree in Animal Science from New Mexico State University and then a Doctorate of Veterinary Medicine from Colorado State University. After an internship at a veterinary practice, he returned to Colorado State University for a PhD in Cell and Molecular Biology with a Special Emphasis in Cancer Biology and a Residency in Veterinary Clinical Pharmacology followed by a junior faculty appointment. In 2016, Dr. Wittenburg accepted a position at the UC Davis School of Veterinary Medicine in Developmental Cancer Therapeutics. The current focus of research in the Wittenburg Lab is investigation of novel therapeutic targets in osteosarcoma, including microRNA and transcription factor complexes and is currently supported through a NIH K01 SERCA award. The Wittenburg Lab also performs research on the pharmacokinetics and pharmacodynamics of anticancer agents and other drugs in veterinary species.

Diedre Reitz, PhD, Postdoctoral Fellow, Department of Microbiology and Molecular Genetics, UC Davis

Diedre Reitz is a postdoctoral fellow mentored by Dr. Wolf-Dietrich Heyer, with co-mentorship from Dr. John McPherson. Her research is focused on Lynch syndrome patients, who are genetically predisposed to cancer. Lynch syndrome patients have abnormalities in the genes encoding the mismatch repair proteins, which is what causes these patients to develop cancer early and often multiple times across their lives. Diedre is using a combination of genetic, genomic, and biochemical approaches to understand how the mismatch repair proteins promote genome stability, and how this regulation is lost in the tumors of Lynch syndrome patients. She was recently awarded the A.P. Giannini Postdoctoral Research Fellowship and Leadership Award to support her research and career development.



PANEL: DIVERSE SCHOLARS FINDING SUCCESS AT UCDCCC (continued)

Alan Lombard, PhD, Assistant Professional Researcher,
Department of Urologic Surgery, UC Davis

Alan received his doctorate in biochemistry, molecular, cellular, and developmental biology from the University of California, Davis in June 2015. He is currently an Assistant Professional Researcher studying advanced prostate cancer. His research focuses primarily on mechanisms of disease resistance in the hopes of developing new therapies aimed at creating better outcomes for cancer patients. He is becoming a thought-leader in the emerging field of PARP inhibition for the treatment of tumors harboring DNA repair deficiency. Alan was among the first to publish research studying how PARP inhibition fits in the prostate cancer treatment paradigm. He has now developed novel models of PARP inhibitor resistant disease which he plans to use to pioneer the field toward understanding acquired PARP inhibitor insensitivity and better defining response and mechanism of action to these exciting therapeutic agents. He recently received an NCI K01 to further study PARP inhibition in prostate cancer. Additional research interests include understanding the contribution of Wnt signaling in driving tumor progression and working to understand cellular lineage plasticity as a mechanism of acquired treatment resistance.



Nicole Coggins, PhD, Postdoctoral Scholar, Genome Center
and Department of Biochemistry and Molecular Medicine,
UC Davis

Dr. Coggins is a post-doctoral researcher in the laboratory of Dr. Luis Carvajal-Carmona at the UC Davis Genome Center. She received her PhD from UC Davis in 2019 in Molecular, Cellular and Integrative Physiology where she developed a novel genome editing platform for the functional modeling of cancer risk-associated variants. During her time as a graduate student, Dr. Coggins was an NIH-IMSD and NIH-MCB T32 fellow. She co-founded the student-lead organization ESTEME, focused on promoting diversity and equity in the STEM disciplines. Her current research as an NCI diversity supplement awardee is now focused on the generation and characterization of pre-clinical models of gastric cancer from underrepresented racial/ethnic minority populations.

SESSION III: Basic/Translational Science

Chair: Luis Carvajal-Carmona, PhD

KEYNOTE LECTURE: THE REPERTOIRE OF MUTATIONAL SIGNATURE IN HUMAN CANCER

Ludmil B. Alexandrov, PhD, Assistant Professor of Cellular and Molecular Medicine and Bioengineering, UC San Diego

Cancer is the most common human genetic disease. All cancers are caused by somatic mutations. These mutations may be the consequence of the intrinsic slight infidelity of the DNA replication machinery, exogenous or endogenous mutagen exposures, enzymatic modification of DNA, or defective DNA repair. In some cancer types, a substantial proportion of somatic mutations are known to be generated by exogenous carcinogens, for example, tobacco smoking in lung cancers and ultraviolet light in skin cancers, or by abnormalities of DNA maintenance, for example, defective DNA mismatch repair in some colorectal cancers.

Each biological process causing mutations leaves a characteristic imprint on the genome of a cancer cell, termed, mutational signature. In this talk, I will present mutational signatures analyses encompassing 30,874 cancer genomes across 91 distinct types of human cancer revealing more than 60 different signatures of mutational processes. Some signatures are present in many cancer types, notably a signature attributed to the APOBEC family of cytidine deaminases, whereas others are confined to a single cancer class. Certain signatures are associated with age of the patient at cancer diagnosis, known mutagenic exposures or defects in DNA maintenance, but many are of cryptic origin. The results reveal the diversity of mutational processes underlying the development of cancer, with potential implications for understanding of cancer etiology, prevention and therapy.

THERAPEUTIC TARGETING OF TUMOR LINEAGE PLASTICITY IN THERAPY-RESISTANT PROSTATE CANCER

Hongwu Chen, PhD, Professor, Department of Biochemistry and Molecular Medicine, UC Davis

Intratumor heterogeneity and lineage plasticity emerge as major mechanisms of therapy resistance, particularly to targeted therapies. In prostate cancer (PCa), tumor cell lineage shifts from adenocarcinoma to neuroendocrine prostate cancer (NEPC) are often observed in patients treated with androgen receptor (AR)-targeting drugs such as enzalutamide or abiraterone. Currently, very few drivers of the lineage transition are identified, which severely hinders the development of therapeutics for overcoming the resistance. Through a focused screening of drugs and compounds for their anti-NEPC activities, we found that several therapeutics that target key epigenetic regulators displayed high potencies, either alone or in combination, in inhibition of NEPC cell growth and survival. Indeed, we demonstrated that the targeted epigenetic writer or reader proteins and their associated transcription factors (TFs) play crucial roles in control of the expression and/or function of key lineage drivers and gene programs such as those of Wnt signaling, cell stemness, and neuroendocrine. Our further studies revealed that pathways of neuronal signaling are among the significantly enriched gene programs downregulated by the treatments. Finally, we found that one major mechanism of action of the therapeutics is reprogramming of key regulatory regions such as enhancers of the lineage drivers or pathways. Therefore, our study identified major epigenetic regulators as new therapeutic targets for therapy resistance-associated lineage plasticity.

SPATIAL RNA PROFILING REVEALS CELL TYPE-SPECIFIC BIOMARKER EXPRESSION DURING MELANOMA DEVELOPMENT

Maija Kiuru, MD, PhD, Associate Professor of Clinical Dermatology and Pathology, Department of Dermatology, UC Davis

Early diagnosis of melanoma is critical for improved survival, but histopathologic diagnosis is inaccurate in a subset of cases. Additionally, biomarkers of early melanoma, including within the

tumor microenvironment, are poorly defined. To address this, we used spatial transcript profiling to measure RNA expression of >1,000 genes in situ in patient-derived formalin-fixed, paraffin-embedded tissue sections from benign and malignant melanocytic tumors. We profiled 200µm-diameter regions of interest (ROIs) enriched in melanocytes (tumor cells), keratinocytes or immune cells. We confirmed distinct expression patterns across cell types and tumor types and identified cell type-specific genes enriched in melanoma. We discovered that keratinocytes within the tumor microenvironment express S100A8 gene in response to melanoma growth and detected prominent keratinocyte-derived S100A8 protein expression in melanoma, but not in benign melanocytic tumors. In addition to identifying S100A8 as microenvironment-specific biomarker in melanoma, our results demonstrate how a spatially resolved gene expression assay can reveal a biomarker's cellular origin and establish a framework for cancer biomarker discovery for diagnosis, prognosis, and response to therapy.

TARGETING EPIGENETIC VULNERABILITIES IN BREAST CANCER

Sanchita Bhatnagar, PhD, Associate Professor, Department of Medical Microbiology and Immunology, UC Davis

Cancer, once thought to be only a genetic disease, is now considered at the crossroads of genetic and epigenetic perturbations. A transformed cell has a profoundly altered epigenetic landscape, mainly dictated by covalent DNA and histone modifications. These abnormalities may arise from mutations in/or altered expressions of chromatin modifiers. We use genome-wide loss-of-function genetic screens and comparative transcriptomic screens to identify and characterize new epigenetic factors malfunctioning in breast cancer. Further, we use this information to develop new therapeutic strategies using antisense oligonucleotide technology, nanoparticles, and small molecule inhibitors.

DISRUPTING THE Rbm38-eIF4E COMPLEX TO INCREASE p53 EXPRESSION AS A POTENTIAL CANCER THERAPEUTIC STRATEGY

Christopher Lucchesi, PhD, Postdoctoral Scholar, Department of Surgical & Radiological Sciences, UC Davis

The p53 tumor suppressor is a transcription factor and stress sensor. Inactivation of p53 has been found to occur in ~50% of human cancers and is a hallmark of tumor progression and chemoresistance. Overexpression of Rbm38, an RNA-binding protein, occurs frequently in a multitude of tumors and is associated with tumor progression potentially through suppression of p53 expression. Functionally, we showed that Rbm38 binds to eIF4E on the p53 transcript and prevents eIF4E from binding to the p53 m7G cap, thereby suppressing p53 mRNA translation. We also showed that disruption of the Rbm38-eIF4E complex by synthetic peptides or small molecule mimics is effective in increasing p53 expression and p53-dependent tumor suppression. These data suggest that modulating the Rbm38-eIF4E complex may be explored as a novel therapeutic strategy for cancers that carry wild-type p53.

ABSTRACTS OF ORAL PRESENTATIONS (FRIDAY)

SESSION IV: Clinical Research

Chair: Karen Kelly, MD

DAVID R. GANDARA LECTURESHIP ON DEVELOPMENTAL THERAPEUTICS: CANCER THERAPY RESISTANCE: MECHANISMS, CHALLENGES AND OPPORTUNITIES

Peter Nelson, MD, Member, Divisions of Human Biology and Clinical Research, Fred Hutchinson Cancer Research Center, Professor, Division of Medical Oncology, University of Washington, Head, Program in Prostate Cancer Research PI, Pacific Northwest Prostate Cancer SPORE

Resistance to cancer-directed treatment is a major obstacle to curing many human malignancies, particularly those that have metastasized from their site of origin. This talk will describe distinct mechanisms that contribute to cancer therapy resistance, illustrate how these mechanisms challenge current treatment paradigms, and describe new approaches designed to exploit particular cancer vulnerabilities exposed by resistance mechanisms.

TRANSLATION OF BLADDER CANCER THERAPEUTICS

Maria Mudryj, PhD, Professor and Vice Chair of Education and Outreach, Department of Medical Microbiology and Immunology, UC Davis

Mamta Parikh, MD, MS, Assistant Professor, Division of Hematology and Oncology, UC Davis

Bladder cancer (BlCa) exhibits a gender disparity where men are three times more likely to develop the malignancy than women. The treatment of advanced bladder cancer, after a long follow period, has been rapidly evolving in the last 5 years, starting with the recognition of benefit of immune checkpoint inhibitor therapy in patients with this disease. Despite this benefit, objective response rates of anti-PD-1 and anti-PD-L1 therapies are modest, and thus a particular area of current interest is evaluating combinations of anti-PD-1 therapy with novel therapies to improve clinical activity. Based on preclinical work done here at UC Davis, we have demonstrated that XPO1 is overexpressed in bladder cancer as compared to normal bladder tissue. Inhibition of XPO1 with the small molecule agent selinexor has demonstrated preclinical antitumor activity in bladder tumors, and in addition, may lead to an increase in PD-L1 expression, suggesting possible synergy in combination with an anti-PD1 agent. We have initiated a clinical trial combining selinexor with pembrolizumab in advanced urothelial carcinoma on the basis of this work and await results.

Numerous studies provide compelling evidence for the involvement of the androgen receptor (AR), but two clinical trials using enzalutamide to target AR were terminated early due to lack of efficacy. We found that BlCa cells express low molecular weight (LMW) AR isoforms that are missing the ligand binding domain (LBD), and isoforms were detected in most BlCa cells rendering them resistant to conventional therapies. However, cells with nuclear AR expression exhibit reduced viability and increased apoptosis on siRNA-mediated AR depletion, hence limiting AR signaling, or AR downstream effectors is an attractive therapeutic strategy. To identify the AR responsive transcriptome, siRNAs were used to deplete all or specific AR isoforms. On depletion of all AR isoforms similar numbers of transcripts are elevated and decreased. Gene ontology analysis found that the most altered biological processes are aging, apoptotic signaling, cell migration, response to endogenous stimuli, and response to oxygen. Molecular functions, biological processes and cellular components associated with decreased transcripts encode proteins involved in various aspects of RNA metabolism, resulting in a decrease of translational components. Coordinately, transcripts elevated on AR depletion are associated with a negative regulation of biosynthetic processes, responses to TGF β and endogenous stimuli, and regulation of apoptosis. Pathway analysis revealed a decrease in transcripts known to promote cancer, including mTOR, transcription factors and

epigenetic modifiers, and mitochondrial components. There is an increase in proapoptotic proteins (HRK, BAK) and a decrease in anti-apoptosis BCL2A1, changes that would lead to a dysregulation of the pro and anti-apoptotic homeostasis with a tilt towards apoptosis. Notably, HIF1 α and multiple HIF1 α pathway components are upregulated on AR-depletion indicative of hypoxia and consistent with mitochondrial dysfunction leading to oxidative stress. Our study identifies AR-dependent alterations in metabolism as an exploitable vulnerability for the design of therapeutics in bladder cancer.

TARGETING THE DNA-BINDING DOMAIN OF THE ANDROGEN RECEPTOR IN CASTRATION RESISTANT PROSTATE CANCER

Paramita Ghosh, PhD, Professor, Department of Biochemistry and Molecular Medicine, Department of Urologic Surgery, UC Davis

Ruiwu Liu, PhD, Research Scientist, Department of Biochemistry and Molecular Medicine, UC Davis

Background: The androgen receptor (AR) plays a predominant role in prostate cancer (PCa) pathology by driving a pro-tumorigenic transcriptional program. Androgen deprivation therapy (ADT) and AR signaling inhibitors (ASIs) can prevent disease progression by inhibiting AR function through direct or indirect inhibition of the AR ligand binding domain (LBD). These remedies are temporary, and upon relapse, patient survival is greatly reduced despite the advent of newer therapies. The goal of the present project is to develop novel therapies that prolong survival. A prominent mechanism of ADT and ASI treatment relapse is the production of alternately spliced AR variants (AR-Vs) that lack the LBD, rendering AR LBD-specific therapies ineffective. On the other hand, the DNA binding domain (DBD) is a prime target for inhibition as it is essential in AR transcriptional activity and is less susceptible to AR alternative splicing compared to the LBD. This project examines a series of novel compounds designed to inhibit AR-DNA interaction and induce apoptosis in castration-resistant prostate cancer (CRPC) cells.

Methods: A series of compounds were designed and synthesized based on hits identified through virtual screening of a large number of compounds against AR DBD in various CRPC cell lines, including C4, C4-2, 22Rv1, CWR-R1 and PC-3. MTT assays were performed to determine the inhibitory effect of compounds on cell viability. Flow cytometry analysis indicated cell death activated by these compounds. Immunoblot analysis, qRT-PCR, and the luciferase assay elucidated the expression of proteins, mRNA and AR transcriptional activity. Immunofluorescence indicated localization of the AR, and the Drug Affinity Responsive Target Stability (DARTS) elucidated the potential binding of the compounds to the target. Studies in intact mice were used to determine toxicity of the compounds and the maximum tolerated dose.

Results: From 22 compounds, 4 were selected for further study based on specificity and the ability to induce cell death. Two of these, C08 and C15, reduces PSA expression. C15, with limited off-target mechanisms of action, induced apoptosis in AR-positive PCa cells and inhibited both AR genomic and non-genomic activity. C15 decreased cell viability in 22Rv1 and CWR-R1 cells (which expressed AR splice variants) to a greater extent compared to C4 and C4-2 (which do not express AR splice variants). Further, this compound had significantly reduced effects in AR-negative PC3 cells and in non-tumorigenic pRNS-1-1 cells expressing wild type AR. Although the compounds did not prevent AR localization in either C4-2 or 22Rv1 cells, C15 significantly reduced AR transcriptional activity compared to DMSO controls in both C4-2 and 22Rv1 cell lines as determined by reporter gene assay. DARTS assay was used to test compound binding to the AR, using enzalutamide as a positive control, and showed that C08 and C15 directly bound to and stabilized full-length AR, and AR variants expressing the DBD, but not a mutant lacking the AR-DBD. C15 showed significantly improved in vitro cell killing compared to the established AR-DBD binding molecule VPC-14449. Studies in intact mice demonstrated no obvious toxicity up to the highest dose tested (50 mg/Kg).

Conclusion: Our preliminary data demonstrate higher efficacy of C15 compared to VPC-14449 as well as the AR-LBD inhibitor enzalutamide in CRPC lines expressing AR-Vs. Based on these results we conclude that C15 is a novel AR-DBD inhibitor with high anti-cancer efficacy, low off-target effects and low toxicity; therefore, it is a promising lead compound for further drug development.

CHARACTERIZATION AND NOVEL TARGETING OF THE AKR1C3/AR/AR-V7 AXIS FOR THE TREATMENT OF LETHAL PROSTATE CANCER

Chengfei Liu, MD, PhD, Assistant Professor, Department of Urologic Surgery, UC Davis

In the United States, prostate cancer (PCa) is predicted to be the second leading cause of cancer related death in men in the United States in 2021. After initial diagnosis of PCa, radical prostatectomy and radiation with or without androgen deprivation therapy (ADT) are used to treat the primary tumors. When cancer recurs, castration-resistant prostate cancer (CRPC) is treated by one of the four Food and Drug Administration (FDA) approved androgen receptor signaling inhibitors (ARSI) enzalutamide (XTANDI®), abiraterone acetate (ZYTIGA®), apalutamide (ERLEADA™) or darolutamide (Nubeqa™). Although these drugs are highly effective initially, patients develop resistance through mechanisms that are not completely understood. Therefore, there is an urgent need to develop strategies to improve the treatment outcome of CRPC. Our research team has shown that genes like AKR1C3, which promotes the production of androgens, are upregulated in PCa cells and xenograft tumors that have stopped responding to enzalutamide and abiraterone. Androgen receptor (AR) negatively regulates AKR1C3 expression possibly through binding with AKR1C3 enhancer in anti-androgen resistant PCa. Reciprocally, AKR1C3 controls AR/AR-V7 protein stability through the ubiquitin proteasome system regulation. In addition, overexpression of AKR1C3 has been detected in clinical metastatic PCa tissues and is elevated by enzalutamide and abiraterone treatments in patients' blood samples. We also developed a novel small molecule inhibitor which showed great potential to synergize with enzalutamide treatment in drug resistant PCa. Thus, targeting AKR1C3/AR/AR-V7 axis is a potential strategy to overcome ARSI resistance.

SOURCE OF FUNDING: This work is supported in part by Paul Calabresi Clinical Oncology K12 Career Development Award (Liu) and grant NIH/NCI R37CA248108 (Liu).

A PHASE 2 NEO-ADJUVANT BIOMARKER DRIVEN CLINICAL TRIAL FOR HIGH-RISK PROSTATE CANCER

Marc Dall'Era, MD, Professor and Vice Chair, Department of Urologic Surgery, UC Davis

Background: Approximately 50% of men will experience disease recurrence after prostatectomy for clinically localized, high risk prostate cancer. Neo-adjuvant clinical trials utilizing androgen suppression, androgen axis inhibitors or systemic chemotherapy have studied the ability of such approaches to reduce disease recurrence and need for additional therapy after prostatectomy. Poly-ADP-ribose polymerase inhibitors (PARPi) are a novel class of anti-cancer agents which have shown some activity against metastatic castrate resistant prostate cancer with DNA repair gene alterations. We initiated a phase 2, neo-adjuvant clinical trial with the PARPi Niraparib for men with newly diagnosed and clinically localized high-risk prostate cancer with deficient DNA repair mechanisms prior to prostatectomy.

Methods: Men with newly diagnosed National Comprehensive Cancer Network (NCCN) high risk prostate cancer and no evidence of metastatic disease on conventional imaging are screened for somatic and germline gene alterations in pathways important for DNA repair. Enrolled men receive Niraparib 300mg orally daily for 90 days prior to undergoing radical prostatectomy. The primary outcome of our study is pathological response after surgery defined as either complete response or minimal residual disease. A secondary outcome is PSA recurrence free survival at 2 years. Tissue and blood before and after treatment is collected for further molecular studies.

Results: The study was activated in January 2020. To date we have screened 35 men and 9 (26%) have met genomic criteria for inclusion. Six men have enrolled in the clinical trial, 4 of whom have undergone prostatectomy. Enrolled men harbor mutations in BRCA2 (germline), CDK12, ATM (2 patients), MSH6 (germline), and ZMYM3. All men have completed 90 days of treatment with Niraparib with 1 grade 3 toxicity characterized by profound thrombocytopenia in a patient with bi-allelic BRCA2 loss.

Conclusions: We successfully initiated a phase 2, biomarker driven, neo-adjuvant clinical trial for men with newly diagnosed and clinically localized high-risk prostate cancer. Multiple challenges exist in executing a biomarker driven trial and thus far approximately 26% of men have met genomic criteria for inclusion. Neo-adjuvant Niraparib appears well tolerated and pathological and disease specific survival results are pending.

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THURSDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>> ENGAGING THE COMMUNITY IN EXPLORER PET: A FEASIBILITY STUDY

Alexandra CT Gori, B.S., Ramsey D. Badawi, Ph.D., Simon R. Cherry, Ph.D., Julie HT Dang, Ph.D., M.P.H., Lorenzo Nardo, M.D., Ph.D., Lynda E. Painting, B.S., Benjamin A. Spencer, Ph.D., Doreen Pichotti, Stephanie Winn, Moon S. Chen, Jr., Ph.D., M.P.H.

The goal of this feasibility study was to initiate and evaluate an approach to promote greater inclusiveness of racial/ethnic minorities to benefit from the world's first total-body PET scanner (EXPLORER) which is affiliated with the UC Davis Comprehensive Cancer Center. This goal is aligned with the National Cancer Institute's call to establish bidirectional relationships between Community Outreach and Engagement (COE) and a basic or clinical science program. For this feasibility study, COE reached out to the Biomedical Technology Program (BTP) to explore whether leveraging COE assets with community stakeholders could synergistically enhance the utility, validation, and dissemination of EXPLORER's radiological and diagnostic capabilities. Through engagement of the cancer center's Community Advisory Board (CAB), BTP invited CAB members to take an actual "ride" on the EXPLORER. CAB members' experiences were video recorded. The cancer center's Senior Public Information Officer also arranged for TV broadcasts and radio stories, reaching thousands of viewers. More than 155 inquiries were received from the public for 20 slots. This was perhaps the first public solicitation using mass media for an IRB-approved clinical trial (NCT04110743) at the UC Davis Comprehensive Cancer Center. Our poster illustrates our bidirectional community engagement process, the experiences the CAB members had during their visit to the EXPLORER facility, and the mass media recruitment methods and responses. Our conclusions were that the CAB and Public Affairs and Marketing team were instrumental in shaping how to reach the public; public response exceeded our expectations; recruitment and engagement of the community approaches were validated.

Acknowledgements and Study ID: NCI support and funding (P30-CA093373-18S4), Primo N. Lara, MD, Principal Investigator
UC Davis IRB: 1714742
ClinicalTrials.gov: NCT04812080

<<2>> CANCER VARIATIONS AND DISPARITIES IN THE CENTRAL VALLEY

Naod Kelete, Julie Dang, PhD, MPH, Frederick J. Meyers, MD, MACP

Cancer incidence and mortality rates vary greatly among the nineteen counties that comprise the University of California, Davis Comprehensive Cancer Center's (UCD CCC) catchment area. Variations may be due in part to differences in social determinants of health (SDOH) including access to education and healthcare, income level, health behavior (e.g., tobacco use, obesity), and food insecurity.

These determinants are major sources of inequalities across the spectrum of cancer prevention and control, defining cancer as both a global health problem and an international health challenge. We used statewide and national surveys to characterize SDOH in UCD CCC's catchment area. We initially examined data from all 19 counties and then performed a detailed comparison of two geographically proximate counties, El Dorado and Yuba. Both counties have a similar cancer incidence rate, but El Dorado has a significantly lower cancer mortality rate. This analysis revealed that El Dorado County has higher levels of education, less smoking, more people per capita with health insurance, more people living above the federal poverty line, and less obese adults in contrast to Yuba County. A better understanding of these characteristics will help us identify individuals and neighborhoods at greater risk and help guide targeted community engaged research.

<<3>> A MINORITY POPULATION FOCUSED OUTREACH EFFORT TO INCLUDE A GREATER PERCENTAGE OF HISPANIC/LATINOS IN THE CANCER CENTER'S 2019 CATCHMENT AREA POPULATION ASSESSMENT

Elizabeth Quino, Fabian Perez^{1,2,3}, Angelica Perez¹, April Vang^{1,2}, Leonie Avendano¹, Julie Dang¹, Moon Chen¹, Alexa Morales Arana^{1,2}, Sienna Rocha^{1,2}, Miriam Nuno^{3,4}, Primo Lara¹, Luis Carvajal-Carmona^{1,2,5}

¹University of California at Davis Comprehensive Cancer Center, Sacramento, CA

²Genome Center, University of California at Davis, Davis CA

³Department of Public Health Sciences;

⁴Department of Surgery,

⁵Department of Biochemistry and Molecular Medicine, School of Medicine, University of California at Davis, Davis, CA

Cancer is the leading cause of death among Latinos, the largest racial/ethnic minority group and the largest group in California. To address challenges experienced by Latinos at the Cancer Center, the Latinos United for Cancer Health Advancement (LUCHA) initiative was established. LUCHA's goal is to pursue cancer health equity among Latinos through bidirectional community engaged research and interventions. A catchment area population assessment (CAPA) was administered by bilingual and bicultural LUCHA staff to understand the local needs and challenges of the community. A primary focus was placed in understanding whether health differences exist between foreign-born and US born Latinos. A total of 255 Latinos within the 19-county catchment area responded to the survey. The majority of survey respondents were foreign-born Latinos (63.9%), female (78.2%), and Spanish speakers (63.2%). Results showed that while the overall respondents reported having health insurance (72.4%), the fraction of uninsured was significantly higher among foreign-born Latinos (38.6% vs. 5.2% in US-born Latinos, $p < 0.001$). When looking at both groups and their rate of preventative screening, it was found that place of birth (whether in the US or Latin America) did not affect cancer screenings. We instead found significant factors to be the time since their last routine check-up in all three cancers ($p < 0.040$ each), education for cervical cancer ($p < 0.003$), and location of health services in breast cancer ($p < 0.050$). To address these findings, LUCHA plans to implement multiple culturally comprehensive cancer prevention interventions and to seek a local support to help mitigate the barriers the Latino community encounters.

<<4>> CHARACTERIZING SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN LATIN AMERICAN COLORECTAL CANCER CASES

Priya Choudhary, Paul Lott, CHIBCHA Consortium, Luis Carvajal-Carmona

Colorectal Cancer (CRC) is the third most diagnosed and third leading cause of cancer death worldwide. Although there are a majority of studies associating risk genes with CRC in non-Latino populations of European descent, there still remains a disparity in studies conducted in Latin American populations. In order to better identify any additional commonly inherited single nucleotide polymorphisms (SNPs) at significant genome-wide association study (GWAS) loci found in these under-analyzed Latino populations, the CHIBCHA (Common Hereditary Bowel Cancers in Hispania and the Americas) consortium was created in order to further reduce the knowledge gap. By integrating gene expression datasets and GWAS of unexamined small CHIBCHA datasets within Brazil, Mexico, and Colombian populations, we report a transcriptome-wide association study (TWAS) analysis via MetaXcan that identifies significant SNPs at new CRC risk loci across populations in these 3 countries. GWAS identified the genetic markers associated with phenotypic variation in CRC. TWAS, a promising new tool, is then used to further investigate and predict associations between gene expression levels and CRC phenotypic variation in each individual in the GWAS cohort. We are currently in the process of conducting pathway analysis, followed by external validation of these results by stratifying with TCGA expression datasets. Therefore, our study provides a better understanding of the causal genes at GWAS loci in these under-studied populations in CRC. This will facilitate the increase of genetic colorectal cancer screening rates in Latino communities, thus aiding to reduce the current disparities present.

<<5>> POLYGENIC RISK SCORE MODELING FOR COLORECTAL CANCER IN LATINOS

April Pangia Vang¹, Paul Lott¹, Luis Carvajal-Carmona^{1,2}

¹ *Genome Center, University of California at Davis, Davis, CA*

² *University of California at Davis Comprehensive Cancer Center, Sacramento, CA*

Colorectal cancer is the third most common cancer in men and second most common cancer in women - and accounted for ~16% of all cancer deaths in 2020. Here, we evaluate the performance of different polygenic risk score (PRS) models and examine how risk variants from predominantly European populations would perform in Latino datasets. We focus on three different colorectal cancer cohorts from Mexico, Colombia, and Brazil with 2,543 cases and 2,579 controls. We constructed the PRS as previously described in past studies where the PRS likelihood ratio was calculated to represent each individual single-nucleotide polymorphism (SNP) using the risk allele frequencies and reported risk odds ratios. Model techniques include Clumping + Thresholding (C+T), forward stepwise regression, and least absolute shrinkage and selection operator (LASSO) regression. We found that European-based PRS models are predictive of Latino datasets. Forward stepwise and LASSO regression models tend to perform better than clumping and thresholding models with the highest area under the curve reaching 0.635 (CI: 0.630-0.039). Our study could be translated with further research into clinics in a cost effective manner that would make it feasible to implement for screening programs within the United States and Latin America.

<<6>> IDENTIFICATION AND ANALYSIS OF GENES ASSOCIATED WITH GASTRIC CANCER IN HISPANIC POPULATIONS THROUGH TWAS

Rasika Venkatesh - UC Davis Genome Center; Giselle Aguayo - UC Davis Genome Center; Paul Lott - UC Davis Genome Center; Luis Carvajal-Carmona - UC Davis Genome Center, UC Davis Comprehensive Cancer Center

Gastric cancer (GC) is the third most common cause of cancer-related death worldwide and limited research has been done regarding its etiology and genetics. Genetics research pertaining to GC is important in alleviating health disparities among minority populations, particularly in Hispanic patients who are twice as likely to contract and die from GC. Towards this end, this study aims to identify novel germline variants associated with GC and determine the prominence of certain genes associated with GC in Colombian and Mexican populations through a transcriptome-wide association study (TWAS). TWAS is a computational technique that enables the identification of protein-coding genes whose expression is significantly associated with complex trait diseases in individuals using expression level information. The primary goal of utilizing this approach is to link splicing and expression level information to functional genes. As the sample populations for the Colombian and Mexican datasets were small, reference data from the GTEX database was used to predict expression level information for prioritized genes and single-nucleotide polymorphisms that may have an effect. Imputed variant-calling files and phenotypic data from Colombian CHIBCHA and Mexico PMRA arrays were incorporated to run a tissue-specific TWAS on stomach and gastroesophageal junction databases using MetaXCan software. Pathway analysis of the genes identified to be genome-wide significant was then conducted to determine if these genes are linked to known or novel oncological pathways. With these results, we hope to identify additional pathways that can be investigated to identify potential drug targets in developing effective treatments for GC.

<<7>> CDH1 AND CTNNA1 VARIANTS WITH INCOMPLETE PENETRANCE IN HEREDITARY DIFFUSE GASTRIC CANCER CHILEAN FAMILIES

Molina G^{1,2}, Estrada AP¹, Pocerros A¹, Coggins N¹, Parra C², Torres O³, Aguayo C³, Norero E^{4,5} Corvalán A^{4,5}, Carvajal-Carmona L^{1,4}.

¹UC Davis Genome Center. University of California-Davis, Davis, USA.

²LINA Facultad de Ciencias de la Salud. Universidad de Playa Ancha, Valparaíso, Chile.

³Servicio de Cirugía Digestiva. Hospital Regional Guillermo Grant, Concepción, Chile.

⁴Esophagogastric Surgery Unit, Surgery Department, Hospital Dr. Sotero del Río, Chile.

⁵Advanced Center for Chronic Disease, Santiago. ⁶Facultad de Medicina. Pontificia Universidad Católica de Chile, Santiago, Chile.

⁶Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis. Sacramento, USA.

The purpose of this study is to describe two Chilean families having Hereditary Diffuse Gastric Cancer (HDGC). Both families present variants of uncertain significance (VUS), that could be pathogenic and causative of cancer in these families but showing incomplete penetrance. Gastric cancer is the leading cause of cancer-related death in Chile. Worldwide, only ten percent of gastric cancer have a familial aggregation and in Hereditary Diffuse Gastric Cancer (HDGC), E-Cadherine 1 gene (CDH1) is the most commonly mutated gene (30%) and CTNNA1 (alpha-1 catenin gene mutations) the second more frequent. The index patient of the first family had a diffuse gastric cancer at 59 years of age. His father and paternal grandfather also died of gastric cancer. A germline variant c.88C>A (p.Pro30Thr, rs139866691) was found previously in the index patient by sanger sequencing. Genotyping of the family members showed that two non-affected sisters presented the same variant. In the second family, there are eleven members affected with gastric cancer and two with breast cancer, in two following generations. The index patient was diagnosed with a diffuse gastric tumor at 51 years of age. Cancer gene panel sequencing was performed in index patient DNA and genotyping in family members was performed. A germline variant c.293G>A (p.R98Q, rs746832629) in the CTNNA1 gene was found in the index patient. We found this variant in two non-affected brothers. Both variants are located in conserved structures of the proteins. The first one in a conserved loop in the E-Cadherine 1 preprotein domain and the second in the first alpha helix of alpha-1-catenin corresponding to beta-catenin binding domain. Based on these, we think that both variants classified as VUS, could be pathogenic and causative of the HDGC observed in these families, but showing an incomplete penetrance. We are performing an isogenic model and functional analysis of both variants to clarify the pathogenicity of them. Beca Chile Postdoctorado 74190063, CONICYT-FONDAP 15130011-2 (NIH).

<<8>> CHARACTERIZING MINORITY PATIENT-DERIVED PRE-CLINICAL MODELS TO ADVANCE GASTRIC CANCER PRECISION HEALTH EQUITY

Nicole B. Coggins, Hongyong Zhang, Paul Lott, Ana Estrada-Florez, Ted Toal, Alexa Morales Arana, Guadalupe Carvajal, Amanda Kirane, May Cho, Javier Torres, Elizabeth Quino, Sienna Rocha, Rasika Venkatesh, Luis G. Carvajal-Carmona.

University of California, Davis, Davis, CA

Mexican Institute of Social Security, Mexico City, Mexico

Gastric cancer (GC) is the third leading cause of cancer-related deaths worldwide. While overall incidence and mortality rates have dropped in recent decades, GC remains a significant health disparity for Hispanic/Latino Americans (HLAs) and Asian Americans, Native Hawaiians and Pacific Islanders (AANHPIs). Despite such high minority cancer burden, few FDA-approved targeted therapies are available for GC. This can be partially explained by limited availability of race-appropriate cancer genome data and minority patient-derived models, limiting target identification and drug efficacy studies. Our group has spearheaded development of the University of California Minority Patient-Derived Xenograft Development and Trial Center (UCaMP) with the goal of addressing these critical issues for GC patient care. In our initial efforts, we have successfully established both patient-derived xenograft (PDX) and organoid (PDO) models for more than 20 minority GC patient samples. Our models recapitulate the molecular landscape of the patient samples from which they are derived. Importantly, multi-omic analyses of minority patient tumor and derived model sets demonstrate high

prevalence of cell cycle regulation/cyclin-dependent kinase (CDK) and PI3K/AKT/mTOR pathway alterations. This is significant, as the FDA has already approved several CDK and PI3K inhibitors for other cancer types and even more show promise in clinical trials. Indeed, when we treat our patient-derived models with these inhibitors, we observe significant responses both in vitro and in vivo. Our findings highlight an important molecular distinction of GC development in racial/ethnic U.S. minorities that provides a rationale for alternative treatments to address GC health disparities.

<<9>> TREATMENT DISPARITIES AMONG PATIENTS DIAGNOSED WITH HIGH GRADE NON-MUSCLE INVASIVE BLADDER CANCER IN CALIFORNIA, 2006-2017

*Eric Stewart, MPH, Onika Noel, MD, PhD², Anshu Shrestha, PhD, MPH¹
Rosemary Cress, DrPH^{1,2}*

Background: Patients diagnosed with high grade non-muscle invasive bladder cancer (hgNMIBC) have the greatest risk of recurrence and disease progression. There is limited data on treatment patterns for early stage disease with high risk of progression.

Purpose: Examine treatment variation among patients diagnosed with hgNMIBC by sociodemographic characteristics.

Methods: Patients diagnosed with hgNMIBC between 2006-2017 were identified from the California Cancer Registry. The sample included patients who received transurethral resection of bladder tumor (TURBT) and were ≥ 20 years of age. Summary statistics, logistic regression and multinomial regression models were used to examine variation in the treatments received.

Results: Of the 14,735 patients identified most were male (81%), older than 70 (60%), and non-Hispanic White (NHW) (77%). Hispanic patients were less likely to receive chemotherapy after TURBT compared to NHW patients, but there was no difference in receipt of immunotherapy (Chemotherapy OR[0.82, 95%CI 0.79-0.96]; Immunotherapy OR[0.94, 95%CI 0.83-1.06]). There was a gradient effect for nSES, showing patients residing in lower SES neighborhoods were less likely to receive any therapy compared to the highest nSES quintile (Lowest OR[0.57, 95%CI 0.50-0.65]). Patients with Medicare or other insurance were less likely to receive immunotherapy after TURBT compared to those with private insurance (Medicare OR[0.71, 95%CI 0.65-0.77]; Other OR[0.73, 95%CI 0.64-0.83]). Unmarried patients were less likely to receive immunotherapy compared to married patients (OR[0.83, 95%CI 0.76-0.90]).

Conclusion: In patients with a diagnosis of high risk NMIBC, disparities in receipt of therapy after TURBT are seen based on race, socioeconomic status, insurance type and marital status.

<<10>> SURVIVAL DISPARITIES AMONG PATIENTS DIAGNOSED WITH HIGH-GRADE NON-MUSCLE INVASIVE BLADDER CANCER (hgNMIBC) IN CALIFORNIA, 2006-2016

*Anshu Shrestha
Anshu Shrestha¹, Onika Noel², Eric Stewart¹, Rosemary Cress,
¹Cancer Registry of Greater California, Public Health Institute, Sacramento, CA
²University of California Davis, Davis, CA*

Background: Survival disparities in patients with high grade non-muscle invasive bladder cancer (hgNMIBC), a fast-growing cancer with higher risk of death, have not been well studied.

Purpose: Examine survival variation among patients diagnosed with hgNMIBC by sociodemographic characteristics.

Methods: Patients diagnosed with hgNMIBC in 2006-2016, who underwent transurethral resection of the tumor (TURBT), were identified from the California Cancer Registry. The sample included individuals ≥ 20 years old with microscopically confirmed first primary cancer. Summary statistics including frequency/%, chi-square tests, Kaplan-Meier curves, and log-rank tests were used to summarize baseline characteristics and overall

survival. Cox proportional and Fine and Gray subdistribution hazard models were applied to assess all-cause and cancer-specific deaths respectively.

Results: Of 15,020 eligible hgNMIBC cases, most were married (61%), non-Hispanic White (NHW, 76%), male (81%), ≥65 years old (75%), and received only TURBT as initial treatment (57%). NH Blacks had higher risk of bladder cancer-specific death (sHR[95%CI]:1.34[1.05, 1.71]) compared to NHWs, but not higher all-cause deaths, even after adjusting for covariates such as neighborhood poverty, comorbidity burden, and initial treatment received. In contrast, Hispanics and Asian/Pacific Islanders had lower risks of all-cause death (HR[95%CI]: 0.91[0.83, 1.00] and 0.87[0.78, 0.96], respectively), but not lower cancer-specific deaths. Findings by other sociodemographic characteristics were similar to previous studies.

Conclusion: There were significant survival disparities in hgNMIBC patients by sociodemographic characteristics. Our findings by race/ethnicity differed from prior findings in similar populations. Further research is needed to confirm and better understand reasons behind these disparities.

<<11>> DEVELOPMENT OF A RESEARCH INFRASTRUCTURE FOR UNDERSTANDING AND ADDRESSING MULTIPLE MYELOMA DISPARITIES

Alexa Morales Arana^{1,2}, Angelica Perez¹, Juanita Elizabeth Quino^{1,2}, April Vang^{1,2}, Fabian Perez^{1,2,3}, Primo Lara¹, Luis Carvajal-Carmona^{1,2,5}

¹ University of California at Davis Comprehensive Cancer Center, Sacramento, CA

² Genome Center, University of California at Davis, Davis CA

³ Department of Public Health Sciences; ⁴ Department of Surgery, ⁵ Department of Biochemistry and Molecular Medicine, School of Medicine, University of California at Davis, Davis, CA

Multiple Myeloma is a malignancy of the plasma cells, that can cause low blood counts, infections, bone and calcium complications, kidney problems among other challenges. In 2018, Multiple Myeloma accounted for nearly 12,326 deaths in the U.S., representing 2.1% of all cancer deaths, with minorities representing 29% of deaths. An effort was put together by the Precision MEDicine, EqUity and Disparities Research in Multiple MyeLoma (MEDULLA) Consortium to begin developing race appropriate recruitment model to better understand and serve as a base for larger population-based studies. In collaboration with the Cancer Registry of Greater California, we received 100 eligible patients from each of the 4 racial/ethnic groups: Black, Latinos, Asian American/Native Hawaiian/Pacific Islander (AANHPI), and Whites who were diagnosed within the 2015-2017. Participants were asked to complete a survey and an optional saliva sample via mailed materials. The survey had a 24% response rate, with the majority being from Non-Hispanic Whites with an overall mean age of 66-years-old. Additionally, while it was not common for respondents to have a family history of Multiple Myeloma or MGUS, 67% reported having a family history of cancer. Findings from this study have yielded insight into the best practices for recruiting in a time of uncertainty with spam calling on the rise, and the ongoing pandemic. Moving forward, we have received approval from UC Davis and State of California IRBs to expand the study to 1,000 patients all over California with all 3 California cancer registries in the next 5 years.

<<12>> THE IMPACT OF THE AFFORDABLE CARE ACT ON HEALTH INSURANCE COVERAGE AND SURVIVAL IN ADOLESCENTS AND YOUNG ADULTS WITH CUTANEOUS MELANOMA

Frances B. Maguire¹, Julianne J.P. Cooley¹, Renata Abrahão^{2,3}, Cyllene R. Morris¹, Arti Parikh-Patel¹, Theresa H. M. Keegan^{1,2}

¹*California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Comprehensive Cancer Center, University of California Davis Health*

²*Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine*

³*Center for Healthcare Policy and Research, University of California Davis School of Medicine*

Background: Adolescents and young adults (AYAs, 15–39 years) remain the most highly uninsured group in the United States. High uninsurance is associated with cancer diagnosed at later stages and higher mortality. We examined the association of the Affordable Care Act (ACA) implementation with survival among AYAs with melanoma in California.

Methods: Data for 8,586 AYAs diagnosed with melanoma from 2005 to 2017 were obtained from the California Cancer Registry and linked to Medicaid enrollment files, providing detailed information on insurance coverage at diagnosis. Period of diagnosis was grouped as pre-ACA (March/2005–September/2010), early ACA (October/2010–December/2013) and full ACA implementation (2014–2017). Multivariable Cox and logistic regression examined associations between ACA, survival, and location of care.

Results: The proportion of younger AYAs (15–25) without insurance (or who acquired Medicaid at diagnosis) decreased from 5.8% pre-ACA to 3.3% post-full ACA but remained unchanged for older AYAs (26–39). Pre- to full ACA, private insurance decreased (76.6% to 60.0%), while continuous Medicaid insurance increased (3.0% to 19.0%). Survival increased post full ACA implementation (HR=0.31; 95% CI=0.12-0.84 for younger AYAs; HR=0.44; 95% CI=0.33-0.59 for older AYAs). Older AYAs were more likely to receive care at National Cancer Institute-Designated Cancer Centers (NCI-Centers) after ACA implementation (OR=1.25 for early ACA; OR=1.39 for full ACA, $p<0.01$).

Conclusion: After ACA implementation, AYAs with melanoma experienced better survival. Younger AYAs had lower proportions of uninsurance; older AYAs had improved access to NCI-Centers. However, more research is needed to better understand the role of new treatments.

<<13>> LATE STAGE CERVICAL CANCER DIAGNOSIS IN YOUNG ADULTS IN CALIFORNIA FOLLOWING THE AFFORDABLE CARE ACT

Julianne J. P. Cooley¹, Frances B. Maguire¹, Renata Abrahão^{2,3}, Cyllene R. Morris¹, Arti Parikh-Patel¹, Theresa H. M. Keegan¹

¹*California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Health, Institute for Population Health Improvement*

²*Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine*

³*Center for Healthcare Policy and Research, University of California Davis School of Medicine*

Background: Young adults (YAs, ages 21–39) may experience barriers to healthcare, including inadequate access to the HPV vaccine and Pap smear test, which can detect pre-malignant lesions or cervical cancer at early stage. Following the Affordable Care Act (ACA), many YAs became eligible for insurance but continued to be diagnosed with later stage cervical cancer.

Purpose: To quantify changes in cervical cancer stage at diagnosis following the ACA and identify characteristics associated with later stage diagnosis.

Methods: Using California Cancer Registry data linked to Medicaid enrollments, we identified 4,244 YAs diagnosed with first primary squamous cell carcinoma (SCC) or adenocarcinoma (AC) cervical cancer pre-ACA (March 2005–September 2010), early-ACA (October 2010–December 2013), and post-full ACA implementation

(January 2014–December 2017). Multivariable logistic regression was used to assess factors associated with later stage diagnosis (AJCC stages II, III, IV).

Results: 31% of patients had AC and 68% SCC; 32% were diagnosed at later stage. From pre- to post-ACA, continuous Medicaid coverage increased 23%, while Medicaid at diagnosis/uninsured decreased by 8%. Later stage diagnosis was associated with Medicaid at diagnosis/uninsured for both AC (OR=2.89, CI 1.88-4.44) and SCC (OR=3.23, CI 2.49-4.20). SCC patients diagnosed post-full ACA expansion (vs pre-ACA) were more likely to be diagnosed at later stage (OR=1.39, CI 1.16-1.68).

Conclusions: Although greater access to the HPV vaccine and screening was expected to improve following the ACA, the proportion of YAs diagnosed at later stages was stagnant over the study period for AC and increased for SCC patients.

<<14>> SECONDARY BREAST CANCER SOCIODEMOGRAPHIC CHARACTERISTICS AND SURVIVAL BY AGE GROUP

Candice A. M. Sauder^{1,2} MD, Qian Li³ MS, Richard J. Bold^{1,2} MD, Kathryn J. Ruddy⁴ MD, and Theresa H. M. Keegan^{3,5} PhD

¹*Division of Surgical Oncology, Department of Surgery, University of California, Davis Medical Center, Sacramento, CA*

²*Comprehensive Cancer Center, University of California, Davis Medical Center, Sacramento CA*

³*Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA*

⁴*Department of Oncology, Mayo Clinic College of Medicine, Rochester, MN*

⁵*Division of Hematology and Oncology, Department of Internal Medicine, University of California, Davis Medical Center, Sacramento, CA*

Background: Secondary cancers account for 16% of all new cancer diagnoses, with breast cancer (BC) the most common secondary cancer. We have shown that secondary BC has unique characteristics and decreased survival compared to primary BC in adolescent and young adults (AYA; 15-39 years old). However, older BC populations are less well-studied.

Methods: Females (age ≥ 15 years) diagnosed with primary BC during 1991-2015 (n=377,167) and enrolled in the California Cancer Registry were compared to those with secondary BC (n=37,625) by age (15-39, 40-64, ≥ 65 years). We examined BC-specific survival (BCSS) accounting for other causes of death as a competing risk using multivariable Cox proportional hazards regression.

Results: Most secondary BC patients were of older age (15-39, n=777; 40-64, n=15,848; ≥ 65 , n=21,000). Compared to primary BC treatment, secondary BCs were more often treated with mastectomy and less often with chemotherapy and/or radiation. BCSS was shorter in secondary BC patients than primary BC patients, but the survival difference between secondary and primary BC diminished with age (15-39 Hazard Ratio (HR): 2.09, 95% confidence interval (CI) 1.83-2.39; 40-64 HR: 1.51; 95% CI 1.44-1.58, ≥ 65 HR: 1.14; 95% CI 1.10-1.19). Survival differences were most pronounced in women with hormone receptor positive disease and Hispanic and Asian/Pacific Islanders 40-64 years of age.

Conclusions: When BC is diagnosed following a prior cancer of any organ site, BCSS is worse than when compared to patients for whom BC is the primary diagnosis, suggesting that we may need to tailor our treatments for women with secondary BC.

<<15>> ASSESSMENT OF PREVIOUSLY REPORTED POLYGENIC RISK SCORE FOR BREAST CANCER IN PERUVIAN WOMEN

Valentina A. Zavala¹, Tatiana Vidaurre², Xiaosong Huang¹, Sandro Casavilca², Jeannie Navarro², Michelle A. Williams³, Sixto E. Sanchez⁴, Bizu Gelaye³, Laura Fejerman^{1,5}

¹Department of Public Health Sciences, University of California Davis, Davis, CA; ²Instituto Nacional de Enfermedades Neoplásicas, Peru; ³Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA; ⁴Universidad Peruana de Ciencias Aplicadas, Lima, Peru and Asociación Civil Proyectos en Salud (PROESA), Lima, Peru; ⁵UC Davis Comprehensive Cancer Center, University of California Davis, Davis, CA.

Genome-wide association studies in individuals of European and Asian origin identified risk-associated loci which can be combined into a polygenic risk score (PRS) to predict breast cancer. We assessed the association of a 313 polymorphism-PRS (313-PRS) previously published and breast cancer risk in women with high Indigenous American ancestry (IAA).

Patients were recruited at the Instituto Nacional de Enfermedades Neoplásicas in Lima, Peru, to be part of PEGEN-BC Study (N=1,755). Women without a diagnosis of breast cancer from PrOMIS Study were included as controls (N=3,342). Genome-wide genotype data were available for all women and missing genotypes were imputed including individuals from the 1000Genomes Project. Logistic regression was used to test the association between standardized PRS residuals and breast cancer risk.

The 313-PRS was associated with breast cancer risk (OR lowest decile vs. intermediate deciles=0.56, 95%CI=0.44-0.71, p= 0.00001; OR highest decile vs. intermediate deciles=1.58, 95%CI=1.27-1.95, p= 0.000035). Analysis stratified by quartiles of IAA did not show heterogeneity. AUROC analysis showed similar estimates for all quartiles of IAA ranging from 0.59 (Q1-lowest ancestry) to 0.61 (Q4-highest ancestry).

We confirmed the association between the 313-PRS and breast cancer risk in highly Indigenous American women from Peru. The magnitude of the association and AUROC were not statistically significantly different by quartiles of IAA. The similarity in the AUROC estimates by ancestry in a study where the highest ancestry quartile (Q4) includes women with more than 91% IAA suggests that PRS developed in mostly European women could be used in Latin-American populations of high IAA.

<<16>> 'TU HISTORIA CUENTA' ONLINE VERSION: PROMOTORES' EXPERIENCE AND PERSPECTIVES ON THE VIRTUAL ADAPTATION OF A HEREDITARY BREAST CANCER EDUCATION AND RISK IDENTIFICATION PROGRAM

Perez, F¹; Robles Garibay, E¹; Perez, A¹; Quino, E¹; Hernandez, M²; Martinez, A³; Castaneda, P²; Ponce, R²; Gonzalez, M²; Martinez, C²; Duron Y⁴; Fejerman L.¹

¹ University of California Davis, Davis, CA

² Vision y Compromiso, Los Angeles, CA

³ Promoters for Better Health, Los Angeles, CA

⁴ The Latino Cancer Institute, San Jose, CA

Breast cancer is the most common cancer in women in the U.S. and the leading cause of cancer related death among U.S. Latinas. Despite having lower breast cancer incidence, U.S. Latinas are more likely to be diagnosed with advanced stage disease compared to non-Hispanic White (NHW) women. This can be attributed to lower rates of screening and longer time to follow up after an abnormal mammogram in the former group. We developed a comprehensive promotores-led education and risk stratification program for Spanish-speaking Latinas to increase mammography screening, genetic testing, and the understanding of the impact of family history on cancer risk. Due to COVID-19 we adapted the program to a virtual platform. This study aimed to record and share the experience from the promotores' perspective as they educated the Latino(x) community through virtual sessions. We used a stakeholder continuous engagement approach and the construct of relational culture to build the program materials. The promotores covered the Sacramento, Los Angeles, and San Francisco areas. All promotores (N=14) in the program were fluent in Spanish and self-

identified as Hispanics/Latinos(x). Through the interviews and informal interaction, promotores shared that virtual platforms alleviated numerous obstacles for attendance like transportation, scheduling conflicts, and childcare costs. However, the online approach removed the personal connection that promotores usually develop with participants. Overall, the experience of transforming the program to a virtual platform provided unique opportunities for bi-directional collaboration between the academic and community partners and with the participants.

<<17>> ELUCIDATING ARSENIC-DEPENDENT CARCINOGENESIS IN HUMAN

*Poceros-Coba Alma A., Department of Biochemistry and Molecular Medicine, UC Davis
Estrada-Flores Ana P., Department of Biochemistry and Molecular Medicine, UC Davis
Toal Ted William, Department of Biochemistry and Molecular Medicine, UC Davis
Lot Paul, Department of Biochemistry and Molecular Medicine, UC Davis
Corresponding author :Carvajal-Carmona Luis G. , Genome Center & Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis*

Arsenic(As) contamination in drinking water is one of the major health issues worldwide. The last two decades this health issue is getting more attention due to the increase of the number of exposed people worldwide. According to an EPA report, around 140 million people were exposed to higher concentrations than the WHO standard in drinking water of 10 ug/L. Several studies indicate that a long lifetime exposure has been associated with the development of carcinogenic changes in Lung, Bladder, Liver, skin cancer and other health problems (Naujokas et al. 2013). The bladder and the lungs are the most affected organs by As toxicity (Yoshida et al. 2004). Genome wide association studies on hotspot populations had indicated association of arsenic metabolism and toxicity impacts at individual and population level (Steinmaus et al. 2014, Agusa et al. 2011). Moreover, several studies suggest that arsenic-related exposure associated with health outcomes relies on the ethnicity and the genetic variation of the populations. Therefore, in this project we compared the somatic mutations identified in bladder cancer tumors from Chilean patients exposed and non-exposed to high levels of arsenic.

<<18>> A CHROMATIN ARCHITECTURE ORGANIZER IN REPROGRAMMING OF CHROMATIN LANDSCAPE IN CASTRATION-RESISTANT PROSTATE CANCER

*Yatian Yang¹, Junjian Wang¹, Hongye Zou¹, Christopher P. Evans², Hong-Wu Chen¹
¹ Department of Biochemistry and Molecular Medicine, UC Davis, School of Medicine
² Department of Urologic Surgery, UC Davis, School of Medicine*

Aberrations in 3D chromatin architecture (e.g. topologically associating domains (TADs) and loops) are implicated in cancer development. Our previous study found that retinoid acid receptor-related orphan receptor γ (ROR- γ), a member of the nuclear receptor (NR) family of transcription factors, functions as a key determinant of androgen receptor (AR) overexpression and aberrant signaling in human castration-resistant prostate cancer (CRPC). However, the mechanism of ROR- γ control of AR function and chromatin landscape in CRPC is unclear. Our ChIP-seq and ATAC-seq-based epigenetic analyses revealed that treatment of CRPC cells with ROR- γ antagonists not only strongly suppressed genome-wide histone acetylation and H3K4 methylation but also markedly decreased chromatin accessibility/openness at enhancer and promoter regions. Interestingly, we also found that the diminished chromatin accessibilities were largely overlapped with AR binding sites and gene activation-linked H3K27ac epigenetic marks. Our further analysis revealed that while ROR- γ inhibition diminished chromatin accessibility at certain genomic loci it also potently induced "open" chromatin structures at specific gene regulatory regions, thus highlighting the remarkable function of ROR- γ in reprogramming chromatin structures. Importantly, we found that DNA binding motifs of a 3D chromatin regulator Brother Of the Regulator of Imprinted Sites (BORIS) is highly enriched in chromatin regions with the reduced accessibility. Knockdown of BORIS markedly downregulated the expression of ROR- γ and AR and inhibited the growth of CRPC cells. Therefore, our work reveals BORIS-ROR γ -AR as a novel regulatory axis in CRPC and provides new insights of the important role of aberrant chromatin architecture in advanced prostate cancer.

<<19>> HOW MISMATCH REPAIR PROTEINS MSH2-MSH3 REGULATE HOMOLOGOUS RECOMBINATION TO PREVENT GENOME REARRANGEMENTS

Diedre Reitz¹, John McPherson², and Wolf-Dietrich Heyer^{1, 3}

¹*Department of Microbiology & Molecular Genetics, University of California, Davis*

²*Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis*

³*Department of Molecular and Cellular Biology, University of California, Davis*

Lynch syndrome predisposes patients to cancer through inherited germline mutations in the genes involved in mismatch repair, including MSH2 and MSH3. The MSH2-MSH3 heterodimer detects large insertion-deletion loops that arise during replication through polymerase slippage, and recruits additional proteins to correct these errors. Furthermore, MSH2-MSH3 function in the regulation of the homologous recombination (HR) DNA repair pathway. This activity of MSH2-MSH3 depends on their ability to detect recombination intermediates containing 3' flaps, formed when the recombination machinery selects a dsDNA donor lacking perfect homology to the broken strand. Given that recombination between non-identical sequences can cause genome rearrangements, this additional function of MSH2-MSH3 suggests that loss of regulation of HR may also drive tumorigenesis in MSH2- and MSH3-deficient patient tumors. However, the precise mechanism through which MSH2-MSH3 regulate HR remains poorly defined.

Endpoint analysis of recombination events involving pairing intermediates with 3' flaps suggests that MSH2-MSH3 have two functions. MSH2-MSH3 recruit effectors to disassemble these intermediates to allow recombination to begin anew (1). When that fails, they engage the nuclease XPF-ERCC1 to mediate flap cleavage (2, 3). Using proximity ligation-based assays developed by our laboratory (4, 5) to examine the HR intermediates on which Msh2-Msh3 are thought to act, my preliminary data indicates that Msh2-Msh3 indeed functions both to disrupt D-loops with 3' flaps, and to promote flap cleavage. Future work includes further in vivo analysis to identify the factors recruited by Msh2-Msh3 to disrupt these mis-paired D-loops and in vitro studies to demonstrate that Msh2-Msh3 specifically recognize D-loops with flaps.

<<20>> BIOENGINEERED miRNA AGENTS ARE MORE EFFICACIOUS AND SELECTIVE THAN CHEMO-ENGINEERED MIMICS IN THE REGULATION OF TARGET GENE EXPRESSION

Neelu Batra^{1,2}, Mei-Juan Tu¹, Ai-Ming Yu¹

¹*Department of Biochemistry and Molecular Medicine, UC Davis School of Medicine; ²AimRNA, Inc., 2700 Stockton Blvd., Sacramento, CA 95817, USA*

Recent investigations have demonstrated the utility of small interfering RNAs (siRNA) and microRNAs (miRNA) as therapeutics for the treatment of many diseases including cancers, viral infections, cardiovascular diseases, and many other disorders. However, current RNAi research and development is limited to the use of chemically synthesized RNA agents that are mounted with various artificial modifications. In this study, we aimed to optimize the tRNA/pre-miRNA-based technology to achieve in vivo fermentation production of fully-humanized bioengineered RNAi agents (hBERA). We first achieved high-level heterogenous overexpression (accounting for >50% of total bacterial RNA) of 20 target hBERAs at 100% success rate, yielding 18-53 mg high-purity ($\geq 98.5\%$) and low endotoxin (< 1.5 EU/ μ g RNA) hBERAs per liter bacterial culture. Further studies demonstrated that target miRNAs (e.g., miR-124-3p) are specifically released from hBERAs in human NSCLC cells to modulate protein levels of targeted genes (e.g., VAMP3 and IQGAP1) and control cell viability. Interestingly, hBERA/miRNAs were more effective and selective than the same concentrations of synthetic miRNA mimics in the control of target gene expression and human NSCLC cell viability. In addition, systemic administration of lipid nanoparticle formulated hBERA had no significant effects on cytokine release in both human PBMCs and immunocompetent mice, as well as hepatic and renal functions. This robust RNA bioengineering platform offers a novel class of fully-humanized, true biologic RNAi agents that are more efficacious than synthetic RNA mimics for research and may be developed as new therapeutics.

<<21>> A NOVEL p73 C-TERMINAL ISOFORM, p73 α 1, REGULATES TUMOR SUPPRESSION AND INFLAMMATION VIA THE NOTCH1 PATHWAY

*Kyra Laubach*¹, *Wenshen Yan*², *Xiangmudong Kong*¹, *Mingyi Chen*³, *Jin Zhang*¹, and *Xinbin Chen*¹

¹*Comparative Oncology Laboratory, Schools of Veterinary Medicine and Medicine, University of California at Davis, Davis, CA, 95616*

²*Current address: Berkeley Regional Lab, Pathology/Lab-Histology Department, The Permanente Medical group, Berkeley, CA, 94085*

³*Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, 75390*

Since it was discovered over 40 years ago, p53 has been recognized as arguably the most critical tumor suppressor. As a transcription factor, this protein regulates the expression of many genes that are involved in preventing the development of cancer. p53 belongs to the p53 family of proteins, which also includes p63 and p73. p73 can produce up to 35 different transcripts, which is the most out of all three family members. While the N-terminal isoforms are relatively well characterized, there is very little known about the function of the C-terminal isoforms. As such, this presentation will focus on the function p73 α 1, a novel p73 C-terminal isoforms. We used cutting edge technology to generate two cancer cell lines that express this isoform, as well as a novel mouse model. Our findings indicate that this novel isoform might have a tumor suppressive function that acts independently of p53. Additionally, we have discovered that p73 α 1 might be responsible for upregulating the pro-inflammatory response via activation of the Notch1 pathway.

<<22>> SOLUBLE CD40L ACTIVATES SOLUBLE AND CELL-SURFACE INTEGRINS ALPHAVBETA3, ALPHA5BETA1 AND ALPHA4BETA1 BY BINDING TO THE ALLOSTERIC LIGAND-BINDING SITE (SITE 2)

Yoko K. Takada^{1,2}, *Michiko Shimoda*¹, *Emanuel Maverakis*¹, *Brunie H. Felding*³, *R. Holland Cheng*⁴, and *Yoshikazu Takada*^{1,2}

The Departments of ¹Dermatology, and ²Biochemistry and Molecular Medicine, UC Davis School of Medicine, Sacramento, California, USA; ³The Scripps Research Institute, Department of Molecular and Experimental Medicine, La Jolla, California, USA; and ⁴Department of Molecular and Cellular Biology, UC Davis, Davis, California, USA

CD40L is a member of the TNF superfamily that participates in immune cell activation. CD40L is an immune checkpoint molecule and a major target for immunotherapy of cancer. CD40L binds to and signals through several integrins, including alphavbeta3 and alpha5beta1 which bind to the trimeric interface of CD40L. We previously showed that several integrin ligands can bind to the allosteric site (site 2), which is distinct from the classical ligand-binding site (site 1), raising the question of if CD40L activates integrins. In our explorations of this question, we determined that integrin alpha4beta1, which is prevalently expressed on the same CD4+ T cells as CD40L, is another receptor for CD40L. Soluble (s) CD40L activated soluble integrins alphavbeta3, alpha5beta1, and alpha4beta1 in cell-free conditions, indicating that this activation does not require inside-out signaling. Moreover, sCD40L activated cell-surface integrins in CHO cells that do not express CD40. To learn more about the mechanism of binding, we determined that sCD40L bound to a cyclic peptide from site 2. Docking simulations predicted that the residues of CD40L that bind to site 2 are located outside of the CD40L trimer interface, at a site where four HIGM1 (hyper-IgM syndrome type 1) mutations are clustered. We tested the effect of these mutations, finding that the K143T and G144E mutants were the most defective in integrin activation, providing support that this region interacts with site 2. We propose that allosteric integrin activation by CD40L also plays a role in CD40L signaling, and defective site 2 binding may be related to the impaired CD40L signaling functions of these HIGM1 mutants.

<<23>> MODULATION OF ANTITUMOR IMMUNITY BY EXTRACELLULAR MATRIX ENVIRONMENT

Claire Robertson¹, Aimy Sebastian², Aubree Hinckley², Naiomy D. Rios-Arce², William F. Hynes¹, Skye Edwards¹, Wei He², Nicholas R. Hum², Elizabeth Wheeler¹, Gabriela G. Loots^{2,3}, Matthew A. Coleman^{2,4}, Monica L. Moya¹

Affiliations:

¹ *Materials Engineering Division, Engineering Directorate, LLNL.*

² *Biosciences and Biotechnology Division, Physical and Life Sciences Directorate, LLNL*

³ *University of California Merced, School of Natural Sciences, Merced, CA, USA*

⁴ *Department of Radiation Oncology, UC Davis, Davis.*

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Emerging evidence suggests that tumor extracellular matrix (ECM) may play a role in tumor-immune interactions, but it remains unclear whether ECM can directly affect the ultimate step in tumor clearance by the immune system, T cell mediated cytotoxicity. We compared clearance of 4T1 mammary carcinoma cells (MCC) seeded on ECM arrays by splenic T cells from MHC mismatched mice (IACUC 290) on different ECM substrates. We found that MCC number significantly decreased in only on Collagen 1, Fibronectin (Fn) and Vitronectin (Vtn) substrates. In Collagen 4 (Col4) containing conditions, MCC cell number increased in the presence of T cells. RNAseq revealed that significance and number of T cell related genes and ontologies were lowest in the Col4 conditions. MCC on Col4 upregulated cytokines including Ccl2, Cxcl3, Cxcl10, and Tgf β 2, compared to both Fn and Vtn conditions, suggesting that this condition could suppress immune activation through altered cytokine expression. In contrast, we observed higher expression of Perforin1 and Caspase 3 in Vtn conditions, but also greater expression of exhaustion related markers such as CD44 and Tim3. In summary, these findings demonstrate that matrix environment can modulate antitumor immunity and that collagen 4 induces a defect in T cell mediated MCC clearance in some ECM conditions that is distinct from the PD-L1 checkpoint.

<<24>> LOSS OF CADHERIN-11 IN PANCREATIC CANCER INDUCES ALTERED IMMUNE CELL INFILTRATION

Kelly A. Martin¹, Aimy Sebastian¹, Nicholas R. Hum^{1,2}, Ivana Peran³, Stephen Byers³, Elizabeth K. Wheeler¹, Matthew A. Coleman¹ and Gabriela G. Loots^{1,2,4}

¹ *Lawrence Livermore National Laboratories, Physical and Life Sciences Directorate, Livermore, CA, USA.*

² *UC Merced, School of Natural Sciences, Merced, CA, USA.*

³ *Georgetown University, Department of Biochemistry & Molecular Biology, Washington, DC, USA.*

⁴ *UC Davis Comprehensive Cancer Center, Sacramento, CA, USA.*

Pancreatic ductal adenocarcinoma (PDAC) is one of the top five deadliest forms of cancer with very few treatment options. The 5-year survival rate for PDAC is 10%, following diagnosis. Mutations in CDKN2A, SMAD4, KRAS and P53 and have been implicated as important drivers in promoting or pancreatic cancer development. Preclinical murine models have been developed that leverage key driver mutations and have significantly contributed to our understanding of PDAC. One such genetically engineered mouse model (GEMM) that has emerged as an important tool in PDAC investigations is the KPC mouse (LSL-KrasG12D/+; LSL-Trp53R172H/+; p48-Cre) that spontaneously develops pancreatic tumors at ~14-16 weeks of age. Cadherin-11 (Cdh11), a cell-to-cell adhesion molecule, has been suggested to play a role in development of the desmoplastic stroma, a characteristic of PDAC, that leads to difficulties in drug accessibility and has been hypothesized to contribute to chemotherapeutic resistance. However, the mechanisms by which Cdh11 deficiency in the stromal microenvironment of PDAC-bearing mice (KPC) influences therapeutic outcomes, has yet to be fully understood.

Single-cell RNA sequencing (scRNAseq) of the immune (CD45+) cellular compartments of tumor bearing (KPC/Cdh11+/+), tumor bearing Cdh11 deficient (KPC/Cdh11+/-), non-tumor bearing Cdh11 deficient (Cdh11+/-) and wildtype (Cdh11+/-) were performed. We observed a sharp decrease in the presence of myeloid/monocyte lineage cells (CD14+) in KPC/Cdh11+/- and also an increase in T, B and plasma cells,

compared to KPC/Cdh11+/+ tumors. Genes upregulated in infiltrating T-cells specific to KPC/Cdh11+/+ mice include *Spp1*, *Ifi30*, *ApoE*, *Ifitm3*, *Fn1*. The increase in B and T cell infiltration was specific to the *Cdh11* deficient background, since both pancreata from KPC/Cdh11+/+ and *Cdh11*+/- mice had elevated levels of infiltration. Immunohistochemical validation of these findings has confirmed these changes in tumor infiltrating immune cells. Future work is needed to clearly define the role of *Cdh11* in modulating B and T-cell behavior in addition to providing insight into *Cdh11* as a therapeutic target for PDAC through altering the tumor microenvironment.

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<<25>> CROSS-SPECIES IMMUNOGENOMIC ANALYSIS IDENTIFIES PATHWAYS OF CANINE NATURAL KILLER CELL RESPONSE TO CYTOKINE THERAPY IN VITRO AND IN VIVO, AND REVEALS CONVERGENCE OF ACTIVATED DOG AND HUMAN NATURAL KILLER TRANSCRIPTOMES

Gingrich A^{1,2}, *Reiter T*², *Judge S*¹, *York, D*³, *Yanagisawa M*¹, *Razmara A*³, *Sturgill I*⁴, *Brady RV*³, *Stoffel K*³, *Monjazeb AM*⁵, *Brown CT*², *Rebhun RB*³, *Canter RJ*¹.

¹Department of Surgery, University of California Davis, Sacramento, CA, 95817

²Department of Population Health and Reproduction, University of California Davis, Davis, CA 95616

³Department of Surgical and Radiological Sciences and William R. Pritchard Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California Davis, Davis, CA, 95616

⁴Department of Dermatology and Internal Medicine, University of California Davis, Sacramento, CA 95817

⁵Department of Radiology, University of California Davis, Sacramento, CA, 95817

Introduction: Natural killer (NK) cells are key effectors of the innate immune system, but major differences between human and murine NK cells impede translation. Outbred dogs offer an important link for NK-based cancer immunotherapy studies. We compared gene expression profiles of dog NK signatures in vitro and from a phase I clinical trial of inhaled IL-15, and analyzed dog, mouse and human NK cells using a novel orthologous transcriptome.

Methods: We performed differential gene expression (DGE) using resting healthy donor CD5dim NK populations and following ex vivo activation using recombinant human (rh)IL-15 or co-culture with irradiated feeder cells. Eight dogs with naturally-occurring pulmonary metastases were enrolled on a Phase I clinical trial of inhaled rhIL-15 using a 3+3 cohort design with escalating doses of inhaled rhIL-15. Blood was collected from study dogs before, during, and after therapy. We compared DGE among healthy and cancer-bearing dogs and then across mouse, dog and human NK cells in resting and activated states using ~7000 1:1 orthologous genes.

Results: DGE revealed distinct transcriptional profiles between the ex vivo resting, IL-15 and co-cultured canine NK cells. Among treated patients, hierarchical clustering revealed that in vivo NK cell transcriptional signatures grouped by individual dog, and not amount of time exposed to treatment. PCA showed in vivo profiles of the clinical responders were distinctly separate from the non-responding patients (PC1 38%, PC2 12%). Patient in vivo NK cell transcription profiles most closely resembled those of ex vivo resting NK cells and not IL-15 treated or co-culture activated (PC1 43%, PC2 19%), likely reflecting key differences in activation. In cross-species analysis, PCA showed within-species spatial clustering of resting NK cells. After activation, variance between dog and human NK cells decreased, while variance between human and mouse NK cells increased (PC1 40%, PC2 28%).

Conclusion: In this first transcriptomic sequencing of dog NK cells, we demonstrate distinct gene profiles of ex vivo activated NK cells from healthy donors compared to circulating NK cells from dogs receiving inhaled rhIL-15 on a clinical trial. Baseline in vivo NK cell profiles appear to predict response to therapy more than changes over time. We also show distinct gene profiles of NK cells across the most commonly used mouse, dog, and human NK populations, with convergence of dog and human NK cells after activation. By defining the canine NK cell DGE signatures, these data fill a gap in translational NK studies.

<<26>> CXCR4/CXCL12 PATHWAY IN MELANOMA PROMOTION FROM TUMOR-PRONE ADULT STEM CELLS

Hyeongsun Moon^{1,2}, *Jane Chen*¹, *William Murphy*^{2,3}, *Alexander Borowsky*^{1,2,4}

¹Center for Immunology and Infectious Diseases, ²Comprehensive Cancer Center, ³Department of Dermatology, ⁴Department of Pathology and Laboratory Medicine, University of California, Davis

Ultraviolet-B (UVB) radiation is the primary carcinogen for cutaneous melanoma. However, the mechanisms of how UVB initiates melanoma promotion from melanoma cells of origin remain unclear. It has been found that adult melanocyte stem cells can act melanoma cells of origin upon expression of oncogenic mutations. Particularly, our previous study found that while tumor-prone adult stem cells in quiescent status remain inactive without significant tumor formation regardless of oncogenic mutation expression, UVB irradiation can significantly induce aberrant activation and translocation of tumor-prone melanocyte stem cells which in turn causes significant tumor formation. Our project uses a novel in vivo model system that permits visualization of UVB-induced melanoma promotion from tumor-prone adult melanocyte stem cells. These stem cells harbor a common melanoma mutation in humans including oncogenic BRAFV600E and PTEN loss of function. When exposed to UVB, these mutant stem cells migrate and form cutaneous melanoma that recapitulates the cutaneous melanoma in humans. Our previous data suggests that significant tumor formation upon UVB irradiation may be through immune-related mechanisms in the tumor-prone stem cell niche. Our preliminary study has pointed to the chemokine, C-X-C ligand 12, CXCL12, in the skin as a compelling contributor of melanoma development. Thus, our current ongoing study aims to define the involvement of CXCL12 and its primary receptor, C-X-C receptor 4, CXCR4, in aberrant translocation of tumor-prone melanocyte stem cells and cutaneous melanoma formation upon UVB irradiation. The study suggests that targeting CXCR4-CXCL12 pathways in cutaneous microenvironment may prevent melanoma promotion from tumor-prone adult stem cells.

<<27>> DEVELOPING A PRE-CLINICAL MODEL OF METASTATIC SOFT-TISSUE SARCOMA

Maria Munoz, Janai Carr-Ascher, UC Davis Comprehensive Cancer Center

In 2021 an estimated 13,000 people will be diagnosed with soft-tissue sarcoma (STS). Unfortunately, 35% of these patients will develop metastasis within 5 years and succumb to this disease. Soft tissue sarcomas arise from mesenchymal stem cells and are diverse, with over 50 subtypes. These include liposarcoma, undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcoma. While the subtypes are histologically and genetically unique, each are capable of metastasizing into the lungs. Their mechanism of metastasis is not fully understood, and little is known about each subtype. Thus, our goals are to develop models of metastatic sarcoma to characterize and compare several STS subtypes and identify mechanisms of metastasis. We developed mouse xenograft models using several STS cell lines, which can metastasize to the lung from primary tumors in the leg. Cells isolated from lung metastases and primary tumors were collected and isolated by magnetic separation and flow cytometry to enrich for human cells. The enriched cells were subjected to RNA-seq to characterize the different subtypes and identify differentially expressed genes that may be important in metastasis. We have identified a list of genes upregulated in the metastatic tumors relative to the primary tumor. This data can help identify future targets to prevent lung metastasis in patients. Overall, the development of this model can help us improve our understanding of STS and potentially identify new therapeutic targets.

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<<28>> ENGINEERED BONE MARROW: A NOVEL MODEL TO INVESTIGATE EARLY STEOSARCOMA PROGRESSION

Katherine H Griffin^{1,2}; Steven W. Thorpe²; R. Lor Randall²; J. Kent Leach^{1,3}

¹*Department of Orthopaedic Surgery, UC Davis Health, Sacramento, CA 95817, USA*

²*School of Veterinary Medicine, University of California, Davis, Davis, CA 95616, USA*

³*Department of Biomedical Engineering, University of California, Davis, Davis, CA 95616, USA*

Osteosarcoma (OS) is the most common primary malignant bone cancer in children and adolescents, yet treatment has remained unchanged for 4 decades and offers less than a 25% 5-year survival rate for those with metastatic disease. This underscores a critical lack of understanding of OS progression and metastagenesis and necessitates the study of this disease in a novel system. Here, we adapt a previously described engineered bone marrow (eBM) construct for use as an improved in vitro model for the study of OS. We also describe early OS loading studies that demonstrate how these constructs will provide a novel 3D platform to study OS tumor progression in future experiments.

eBM was loaded with a highly metastatic OS cell line, K7M2, and cultured under 21% and 5% O₂. Metabolic activity and flow cytometry for progenitor cell and macrophage populations were evaluated. We found that eBM accurately recapitulated native mouse bone marrow and that maintenance in ex vivo culture was most stable under normoxic (5% O₂) conditions. eBM loaded with K7M2s exhibited decreased metabolic activity only when cultured under 21% O₂, and macrophages of M1 polarization decreased under all conditions whereas M2 populations did not change.

The eBM in this project accounts for the complex environment in which OS arises, thereby surpassing previous in vitro models that fail to account for these key parameters. Moreover, this model facilitates the enhanced study of OS pathophysiologic progression that leads to metastagenesis and will thus advance the treatment of patients afflicted by OS.

<<29>> OPTIMIZATION OF EXPANSION TECHNIQUES FOR ADOPTIVE NK CELL TRANSFER IN DOGS WITH CANCER

Aryana M. Razmara, Sean J. Judge, Cordelia Dunia, Robert B. Rebhun, Michael S. Kent, Robert J. Canter
Department of Surgery (Razmara, Judge, Dunia, Canter), School of Medicine, UC Davis, Sacramento, California. Department of Surgical and Radiological Sciences (Rebhun, Kent), School of Veterinary Medicine, UC Davis, Davis, California.

Natural killer (NK) cells can recognize heterogeneous cancer cell targets without prior sensitization, making them promising prospects for use in immunotherapy. We have completed first-in-dog feasibility clinical trials in dogs with cancer using both autologous and allogeneic NK cells expanded from peripheral blood mononuclear cells (PBMCs). Previously, CD5 depletion of PBMCs has been used to enrich for a CD5^{dim} expressing subset prior to NK co-culture with an irradiated feeder line, but this can limit the yield of the final NK product. The purpose of this study was to compare ex vivo culture conditions using standard CD5 depletion versus unmanipulated PBMCs plus feeder line co-culture in matched healthy donors, hypothesizing that PBMCs plus feeder cells would generate an equivalent or superior NK product to CD5 depletion. A mixed-effects model analysis showed no statistical difference in calculated cell counts, overall fold change, and viability ($p > 0.05$ all) between PBMCs with feeders and CD5 depleted cells with feeders. PBMCs had a higher mean than CD5 depleted cells at day 14 in all three categories, reaching a peak mean of 677 million cells from 5 million PBMCs at day 0. Killing assays against melanoma and osteosarcoma targets and immunophenotyping also demonstrated comparable results among PBMCs plus feeders versus CD5 depleted NK cells ($p > 0.05$). Overall, these findings support the use of unmanipulated PBMCs plus feeder line co-culture as an equivalent method to CD5 depletion in the expansion of canine NK cells for adoptive immunotherapy.

FRIDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>> FIBI, A DIRECT-TO-DIGITAL MICROSCOPY APPROACH FOR SLIDE-FREE HISTOLOGY

Farzad Fereidouni, Taryn Morningstar, Arshia Rangchi, Tanishq Abraham, Alexander Borowsky, Richard Levenson, Department of Pathology and Laboratory Medicine, UC Davis Health, 4400 V Street, Sacramento, CA 95817

Anatomic pathology, still the gold standard for tissue-based disease diagnosis, is centered on interpretation of H&E-stained sections on glass slides, a process that has remained largely unchanged for at least a century. Current methods require labor-intensive and time-consuming specimen processing steps that are ill-suited for providing rapid intraoperative guidance and margin assessment, especially for breast surgeries, and are not capable of generating high-quality, histological (not cytological) rapid onsite evaluation of core needle biopsies. Current approaches for bypassing slide-based imaging have encompassed a variety of technologies, including confocal, multiphoton, and other optical methods, but these have yet to have significant impact in the field due to challenges posed by cost and complexity issues. We propose a simple, clinically relevant solution, termed FIBI (fluorescence imitating brightfield imaging), for directly creating diagnostic-quality images from unsectioned, fresh or fixed tissue specimens. FIBI can generate full-color histology-grade images within minutes using inexpensive components making it suitable for intraoperative guidance and cancer margin assessment, especially for breast surgeries.

<<2>> COMBINATORIAL HIGH-THROUGHPUT KINASE SCREENING ENABLED BY A MICROFLUIDIC PRINTING ROBOT

Chuqing Zhou¹, Jiyoung Shim¹, Zecong Fang^{1,2}, Conary Meyer¹, Ting Gong¹, Matthew Wong¹, Cheemeng Tan¹, Tingrui Pan^{1,2,3}

¹*Department of Biomedical Engineering, University of California, Davis, California, 95616, USA*

²*Institute of Biomedical and Health Engineering, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, 518055, China*

³*Suzhou Institute for Advanced Research, University of Science and Technology of China, Suzhou, 215123, China*

#CZ and JS contributed equally.

**corresponding authors*

Protein kinase pathways are popular drug targets because their disorder can cause cancers. To find effective drugs, a single kinase is typically screened with drug candidates in vitro. Yet, the context of the kinase pathways is known to affect the efficacy of drugs. Here, we engineer a microfluidic printing platform for the high-throughput assembly and screening of a kinase pathway in vitro. The platform prints 1000s of nanoliter droplets of kinase and buffers with an accuracy of 96.3%. The platform allows for precise control over the concentration and combination of the kinases. We demonstrate the platform using a sub-network of mitogen-activated protein kinase consisting of MEK and ERK. Furthermore, we screen for selective membrane attachment of the kinases. We find that the kinase activity of a MEK1 mutant is dominant compared to that of ERK2 WT, and ATPase activity increases with higher concentrations of both protein kinases. Our robotic platform enables combinatorial assembly and screening of protein networks, paving the way towards pathway-based screening of drugs in vitro.

<<3>> REAL-TIME INTRAOPERATIVE FLUORESCENCE LIFETIME IMAGING OF 5-ALA INDUCED PpIX AND AUTOFLUORESCENCE IN BRAIN TUMORS: FIRST RESULTS IN PATIENTS

Silvia Noble Anbunesan¹, Xiangnan Zhou¹, Alba Alfonso Garcia¹, Julien Bec¹, Farzad Fereidouni², Lisanne Kraft¹, Roberto P. Frusciante¹, Lee-Way Jin², Han Sung Lee², Orin Bloch³, Laura Marcu^{1,3}

¹Department of Biomedical Engineering, University of California Davis, One Shields Avenue, CA, 95616, USA

²Department of Pathology and Laboratory Medicine, University of California Davis, 4860 Y St, Sacramento, CA, 95817, USA

³Department of Neurological Surgery, University of California Davis, 4860 Y St, Sacramento, CA, 95817, USA

Intraoperative fluorescence-guided surgery (FGS) using 5-aminolevulinic acid (5-ALA) induced protoporphyrin IX (PpIX) has enabled neurosurgeons to optimize tumor resection of malignant gliomas. Approved for clinical use in both Europe (2007) and USA (2017), 5-ALA fluorescence in glioblastoma is strong enough to be observed using a surgical microscope with dedicated 405nm light source but detecting glioblastoma's infiltrative edges as well as lower grade gliomas and brain metastasis is limited by the lower fluorescence intensity. We propose using fluorescence lifetime imaging (FLIm) to enhance the detection of exogenous 5-ALA induced PpIX and endogenous metabolic cofactor NAD(P)H in GBM infiltrative edges. A FLIm instrument (355nm excitation, ~0.25μJ, 600ps, 480Hz) was used for in-vivo scanning of brain tumor and surrounding healthy tissue in 3 patients. The recorded fluorescence signal was spectrally resolved into 3 bands (390/40nm (collagen), 470/28nm (NAD(P)H), and 629/53nm (PpIX)) with real-time (<10μs) fluorescence lifetime computation. In-vivo data acquired from infiltrated cortex surface revealed high PpIX accumulation associated with tumor areas (>8 ns) compared to healthy brain tissue (<4 ns). Higher NAD(P)H lifetime (~5.5ns) was also observed in the tumor region compared to surrounding healthy tissue (~3 ns). These results demonstrate that endogenous and exogenous signals can be used in conjunction to investigate changes in tissue metabolism that may lead to improved detection of tumor infiltration to supplement decreased performance of visible 5-ALA fluorescence. These results encourage the further development of intraoperative FLIm of 5-ALA induced PpIX and tissue autofluorescence as a surgical adjuvant tool to guide tumor resection in real time.

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<<4>> THERMO-RESPONSIVE pNIPAM NANOPARTICLES IMPROVE PIPLARTINE CYTOTOXICITY IN 3D BREAST TUMOR MODELS AND REDUCE TUMOR DEVELOPMENT IN VIVO UPON INTRADUCTAL ADMINISTRATION

Vanessa F. C. Dartora¹, Marcus Deloney¹, Luciana B. Lopes², Alyssa Panitch¹

¹Biomedical Engineering - University of California Davis

²Institute of Biomedical Sciences - University of Sao Paulo

In this work, we propose the development of nanocarriers for intraductal drug administration for local management of non-invasive, low grade ductal carcinoma in situ (DCIS) and atypical lesions. Aiming to obtain a prolonged drug retention and localization, we synthesized a thermoresponsive poly(N-isopropyl acrylamide) nanoparticle (NP) delivery system to encapsulate and localize the chemotherapeutic agent piplartine and the anti-inflammatory peptide inhibitor of MAPKAP Kinase 2 (MAPK2), YARA (MMI-0100), directly at the mammary glands. The NP cytotoxicity was evaluated in spheroids (3D culture) of breast cancer cells (MCF-7 and T47-D) after 48 h of treatment. Subsequently, NPs in vivo efficacy was assessed in a chemical model of carcinogenesis (MNU) using female sprague-dawley rats 8 weeks-old. Compared to the drug in solution (IC50 133.8μM in MCF-7 and 105.0μM in T47-D), piplartine-containing NP reduced the IC50 up to 4.9 times. The combination of piplartine and YARA in NP further reduced the piplartine IC50 (~15 times). Palpable tumors developed in 77.7% of the animals in the induced non-treated (2.5 ± 1.6 tumors/animal) group, while treatment with NP reduced the tumor incidence by 6.5 times. These results were confirmed through histological analysis. The piplartine detected in the mammary glands treated with NP (35.3 ± 22.4 μg /mL) was 50-times more than piplartine quantified in plasma, showing that the nanocarrier allow most of the drug to be retained in the breast tissue. These results demonstrate that the nanocarrier was able to reduce tumor development after MNU

induction, with low systemic exposure following NP intraductal administration, corroborating the results in spheroids. This unprecedented combination may represent a new therapeutic strategy to for localized DCIS treatment.

<<5>> SAFETY AND EFFICACY OF INTRAVENOUS BISPHOSPHONATES FOR TREATMENT OF HYPERCALCEMIA OF MALIGNANCY IN PATIENTS WITH BASELINE RENAL DYSFUNCTION

Ryan J Beechinor, PharmD, BCPS, BCOP

Emily H Hsu, PharmD, UC Davis Medical Center, Sacramento, CA, 95817, USA

Hypercalcemia of malignancy (HCM) is a potentially life-threatening metabolic complication of cancer. Intravenous (IV) bisphosphonates are first-line agents for HCM, but studies examining their use in patients with renal dysfunction are limited. We compared the safety and efficacy of IV zoledronic acid and IV pamidronate for HCM in patients with and without renal dysfunction. Adults (≥ 18 years old) hospitalized with HCM and treated with IV bisphosphonates were identified retrospectively. The primary safety outcome was all-grade serum creatinine (SCr) elevation by day 7. The primary efficacy outcome was complete response (CR), defined as normalization of corrected serum calcium (CSC) ≤ 10.5 mg/dL, by day 10. Patients with and without renal dysfunction were defined by creatinine clearance (CrCl) ≥ 60 mL/min and CrCl < 60 mL/min, respectively. Primary statistical analyses were performed using Fisher's exact test. A total of 100 patients were included in this analysis (n = 50, with renal dysfunction; n = 50, without renal dysfunction). There was no statistically significant difference in all-grade SCr elevation or CR by day 10 with respect to bisphosphonate received or baseline renal function. The primary safety outcome of all-grade SCr elevation occurred in 28% (18/50) of patients with renal dysfunction and 36% (14/50) of patients without renal dysfunction ($p = 0.52$). The primary efficacy endpoint of CR by day 10 occurred in 78% (39/50) of patients with renal dysfunction and 66% (33/50) of patients without renal dysfunction ($P = 0.13$). Future studies are needed to inform optimal bisphosphonate therapy in this patient population.

<<6>> FULLY-HUMANIZED BIOENGINEERED miR-1291 MODULATES KEY NUTRIENT TRANSPORT AND METABOLISM TO EXERT SYNERGISTIC ANTICANCER EFFECTS WITH CHEMOTHERAPEUTICS

Mei-Juan Tu, Zhenzhen Liu, Linglong Deng, Chao Zhang, Ai-Ming Yu

Cancer cells generally rely more heavily on vital exogenous nutrients than normal cells to meet energetic and material needs for high-rate proliferation and tumorigenesis. Therefore, control of nutrient transport and metabolism in cancer cells is a novel anticancer strategy. Our previous studies have suggested that microRNA-1291-5p acts as a tumor suppressor in pancreatic cancer (PC). The current study aimed to develop a new approach to produce and employ fully-humanized recombinant miR-1291 agent to investigate its mechanistic actions in the regulation of PC cell metabolism and combination therapy with other metabolic modulators. We first cloned and achieved high-level expression of humanized recombinant htRNASer/miR-1291 using human serine-tRNA as a carrier. Deep sequencing analyses revealed that htRNASer/miR-1291 was selectively processed to miR-1291-5p in PC cells. PNPO, an vitamin B6 (VB6) synthesis enzyme, was revealed as a leading target of miR-1291-5p by proteomics study. In addition, transporter SLC7A5/LAT1 was verified as a direct target for miR-1291-5p. Downregulation of PNPO, LAT1, GLUT1 protein expression by biological miR-1291 led to sharp alteration of homeostasis of glucose, amino acids, and VB6 in human PC cells, and subsequently an increase of oxidative stress. Subsequently, the glycolysis capacity and mitochondrial function of PC cells were significantly suppressed as demonstrated by Seahorse analyses. In addition, combination treatment with htRNASer/miR-1291 and 5-FU exerted synergism in the inhibition of PC cell growth. Overall, our studies revealed a critical role of miR-1291 in the regulation of PC cell metabolism which may provide novel insight in developing new therapeutic strategies for PC.

<<7>> INHIBITING SOLUBLE EPOXIDE HYDROLASE AS A TREATMENT FOR CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHIC PAIN

*Karen Wagner, Sung Hee Hwang, Bruce D Hammock
University of California Davis*

The pain of chemotherapy induced peripheral neuropathy (CIPN) is one of the most common reasons that cancer patients stop their treatment early. Chronic pain is a life altering debilitating condition that remains inadequately treated today. Investigating the broader efficacy of sEH inhibition has indicated that it would be efficacious in chemotherapy induced peripheral neuropathy (CIPN). This painful neuropathy develops most frequently from platinum containing, vinca alkaloid and taxane based chemotherapeutics, is notoriously difficult to treat, and can lead to discontinuation of life-prolonging cancer treatments. We tested the efficacy of small molecule inhibitors of soluble epoxide hydrolase inhibitor for their efficacy in models of CIPN and to characterize their analgesic potential. Our results revealed that oral dosing of sEH inhibitors were dose dependently effective against CIPN pain in all three of the included models. In addition, potential motor side effects of sEH inhibition were assessed in an open field assay which revealed no changes from baseline when treated compared to pretreatment baselines.

<<8>> ASSOCIATION BETWEEN BREAST CANCER POLYGENIC RISK SCORE AND TUMOR SUBTYPE IN HIGHLY INDIGENOUS AMERICAN WOMEN FROM PERU

Ravinder Singh¹, Valentina Zavala¹, Xiaosong Huang¹, Sandro Casavilca-Zambrano², Tatiana Vidaurre², Laura Fejerman¹;

¹University of California at Davis, Davis CA

²Instituto Nacional de Enfermedades Neoplasicas, Lima, Peru

Breast cancer is the first leading cause of cancer death in Hispanic/Latina women. Genetic variants discovered in European and Asian populations can be used to predict risk in Hispanics/Latinas. The objective of this project was to test the association between a previously reported 313-polymorphism breast cancer risk score (313-PRS) and tumor subtype in Peruvian breast cancer patients. The Peruvian Genetics and Genomics of Breast Cancer Study recruited women of 21-79 years of age with a diagnosis of invasive disease from Lima, Peru. Electronic medical records were used to abstract demographic and clinical information. Genotype data for the 313-PRS and genetic ancestry estimations were obtained with the Affymetrix PMR Array. We used t test, analysis of variance and logistic regression to assess association. ER/PR+ HER2- was the most common breast cancer subtype (49.6%) followed by ER/PR+ HER2+ (17.3%), ER/PR- HER2+ (12.5%) and ER/PR- HER2- (14.9%). The average PRS was higher in women with ER/PR+ compared to ER/PR- disease (t-test, p-value for ER= 0.00075 and for PR 0.00295) with no difference by HER2 status (p= 0.9249). The odds of ER+ disease increased by 1.42 for every unit increase in the 313-PRS (95%CI= 1.42; 1.18-1.71, p value= 0.000169), including age and Indigenous American ancestry as covariates. A previously reported PRS for breast cancer prediction is positively associated with ER/PR status in Peruvian breast cancer patients. Future studies should include larger proportion of diverse patients with ER/PR- subtypes as to improve prediction of aggressive disease.

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<<9>> PATIENT NAVIGATORS' IMPACT ON CANCER SCREENING FOR LIMITED ENGLISH PROFICIENT PATIENTS

Khadija Soufi, UC Davis SOM, MS2

Tess Perez, UC Davis, MS2

Dr. Rashmi Verma, UC Davis Faculty, Comprehensive Cancer Center

BACKGROUND: 20.3 % of the U.S. population speak a language other than English at home; nearly 25 million reported that they have limited English proficiency (LEP) (1). These patients face detrimental health disparities as their access to health care, especially cancer screening, is limited. Minority ethnic groups with LEP have lower rates of cancer screening and higher death rates from preventable types of cancer including breast, colorectal, cervical, prostate and lung cancers. We hypothesize that patient navigators will positively impact the screening rates of LEP patients.

PURPOSE: The purpose of patient navigation is to ameliorate barriers to timely diagnosis and treatment of cancer. This study aims to identify how a patient's willingness to participate in cancer screening measures with due consideration of language and cultural barriers by health care providers. We are also aiming to improve patient's attitude towards cancer screening.

METHODS: This is a prospective ongoing survey study used to screen for patient-identified cultural communication barriers, including language barriers, and evaluate how addressing those barriers can increase cancer screening compliance. The survey was administered at Shifa Community Clinic, a student run clinic, providing free multilingual, multicultural healthcare service to underserved communities.

RESULTS: Questionnaire has been administered to 30 low income patients - 55% of participants were foreign born immigrants and 30% were refugees. Our patient's ethnic background included 47% Asian, 21% Middle Eastern and 15% Hispanic. Results showed increased patient compliance with screening when patients were counseled in their native language due to increased trust and better understanding.

<<10>> TETRASPANINS ARE UNEVENLY DISTRIBUTED ACROSS SINGLE EXTRACELLULAR VESICLES AND BIAS SENSITIVITY TO MULTIPLEXED CANCER BIOMARKERS

Rachel R. Mizenko¹, Terza Brostoff², Tatu Rojalin¹, Hanna J. Koster¹, Hila S. Swindell³, Gary S. Leiserowitz⁴, Aijun Wang^{1,3}, Randy P. Carney¹

¹*Department of Biomedical Engineering, University of California, Davis, United States,*

²*Department of Pathology, University of California, San Diego, United States,*

³*Department of Surgery, University of California, Davis, United States,*

⁴*Division of Gynecologic Oncology, University of California Davis Medical Center, Sacramento, California, United States*

60% of ovarian cancer (OvCa) patients are diagnosed at stage III or IV, where 5-year survival rates are below 40%. A new diagnostic platform is necessary to increase sensitivity to OvCa markers at earlier stages. Extracellular vesicles (EVs), membrane bound nanoparticles secreted by cells, have been suggested as a novel diagnostic target due to their presence in biofluids and altered protein expression from cancerous cells. Current EV diagnostic platforms use tetraspanins, EV associated membranous proteins, to capture EVs prior to probing for disease markers. However, tetraspanin expression varies significantly between EVs from different sources. Here, we identify how capture by a single tetraspanin could affect sensitivity to OvCa markers, and how this can be mitigated by non-specific capture.

OvCa EVs were captured by a microarray of antibodies against tetraspanins (CD9, CD63, or CD81) and labeled with fluorescent antibodies for tetraspanins or OvCa markers and imaged by fluorescence microscopy. To decrease protein bias, EVs were biotinylated and captured by anti-biotin. Fluorescence microscopy of tetraspanin-captured EVs confirmed that tetraspanins do not colocalize homogeneously on single EVs indicating tetraspanin expression subpopulations. Furthermore, capturing non-specifically by anti-biotin revealed that single-tetraspanin capture could bias the apparent multiplexed tetraspanin profile. Finally, when detecting

OvCa markers on EVs, CD24 could only be identified by CD9 or non-specific capture, and EpCAM and Her2 detection were more sensitive by non-specific capture.

This work demonstrates that tetraspanin capture can limit diagnostic sensitivity, while non-specific biotinylation may allow for less biased multiplexed protein analysis of EVs in future studies.

<<11>> CURATION OF TCGA TREATMENT DATA FOR GENOMIC PREDICTION OF DRUG RESPONSE IN OVARIAN CANCER

Dennis J. Montoya¹, Sydney Woods¹, Jeremy Chien^{1,2}

¹*Department of Biochemistry and Molecular Medicine, UC Davis Medical Center, Sacramento, CA, USA.*

²*Department of Obstetrics and Gynecology, University of California Davis Medical Center, Sacramento, CA*

Background: The Cancer Genome Atlas (TCGA) is a comprehensive database of cancer genomic profiles which has democratized access to genomic analysis of cancer and allowed associations with clinical outcome. Although the treatment regimen can confound patient outcome analysis, the TCGA pharmaceutical annotation is often ignored in most studies. Here, we curate the treatment data of the ovarian cancer cohort (TCGA-OV) to study the resistance to platinum chemotherapy.

Results: After extensive standardization of the pharmaceutical data, we found the majority of patients had the standard adjuvant treatment, composed of a platinum-based agent with a taxane agent. However, a large subgroup of patients was given other treatments that had a significant difference in overall survival depending on the drug class used. For patients given standard therapy, the route and type of platinum agent affected survival outcome. For example, patients given intraperitoneal cisplatin had increased survival compared to those given intravenous carboplatin. Accounting for the treatment heterogeneity, we were able to categorize resistance to platinum therapy through calculation of the platinum-free interval (PFI) until progression of disease.

Discussion: Our data identify significant heterogeneity in the treatment regimen across TCGA-OV, corresponding to significant differences in patient outcome. Our curation allows reduction in this heterogeneity to allow categorization of the drug response to platinum chemotherapy agents. Further study will compare the genomic profiles of the response categories to identify pathways and markers associated with platinum resistance. Our study also suggests careful use of TCGA outcome data without first accounting for treatment heterogeneity.

<<12>> LLC1, A NOVEL HYDROPHOBIC AMILORIDE DERIVATIVE, TARGETS BREAST CANCER CELLS VIA ROS-INDUCED LYSOSOME-DEPENDENT CELL DEATH

Michelle Hu, Yashvi Deokule, Ruiwu Liu, Kit S. Lam, and Kermit L. Carraway, III

Department of Biochemistry and Molecular Medicine, and Comprehensive Cancer Center, UC Davis School of Medicine, Sacramento, CA 95817

We have previously shown that hexamethylene amiloride (HMA), a hydrophobic derivative of the potassium-sparing diuretic amiloride, specifically kills breast cancer cells independent of molecular profile while leaving non-transformed cells unharmed. HMA triggers lysosomal membrane permeabilization (LMP), or the breaching of the limiting membrane of the lysosome, to activate a unique programmed necrotic cell death mechanism called lysosome-dependent cell death (LDCD). Here we begin to optimize hydrophobic derivatives of amiloride, seeking to increase drug potency while maintaining tumor cell-specific cytotoxicity. After screening eight newly designed and synthesized amiloride derivatives, we demonstrate that derivative LLC1 exhibits substantially greater potency toward breast cancer cells than HMA. We observe that LLC1 engages a reactive oxygen species (ROS)-dependent mechanism of LMP induction, and confirm the cancer selectivity of LLC1 ex vivo using tumor and mammary organoids. Finally, we observe that heat shock protein 70 (HSP70) can protect cells against amiloride derivative-induced LMP. Our observations suggest that amiloride derivatives might be repurposed to attack multiple tumor cell subtypes by engaging necrotic signaling via ROS without damaging normal tissue.

<<13>> MARCKS-REGULATED ENDOPLASMIC RETICULUM STRESS RESPONSE CONTRIBUTES TO MACROPHAGE POLARIZATION IN LUNG CANCER PROGRESSION

Chih-Wei Chu, Ji-Min Li, Madison Luker, David Yang, Wen-Hsin Chang, Ssu-Wei Hsu, Ching-Hsien Chen
Divisions of Nephrology and Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine,
University of California, Davis, CA.

Perturbation of endoplasmic reticulum (ER) homeostasis leads to aggregation of unfolded proteins in the ER lumen and induces ER stress. Dysregulated ER stress responses in cancer cells have been recently reported to modulate tumor progression and the tumor immune microenvironment; however, the mechanisms of how the ER stress response pathways in tumors coordinate with immunity remain to be elucidated. The oncogenic receptor AXL has been identified as a therapeutic target for lung cancer, and we previously demonstrated that myristoylated alanine-rich C kinase substrate (MARCKS), highly expressed in aggressive lung cancer, forms a molecular complex with AXL. Our current work showed an accumulation of AXL in the ER lumen upon knockdown of MARCKS. Genetic manipulations and pharmacological approaches revealed that MARCKS expression participates in activation of ER stress sensors, predominantly IRE1 α and PERK, and their downstream proteins in lung cancer cells, in agreement with our observations in the integrated transcriptome analysis and functional proteomics. Notably, several IRE1 α -driven pro-inflammatory and immunomodulatory cytokines, such as CXCL1, GM-CSF, and IP-10, were up-regulated in MARCKS-knockdown cells. Upon co-culturing macrophages derived from human monocytic cells with lung cancer cells, we found a remarkable increase of ER stress responses in MARCKS-knockdown cells. In addition, we noticed a lower proportion of M2 macrophages from the MARCKS-knockdown group. Xenograft tumor models confirmed that MTAP-proficient tumors display greater tumor size and a higher number of tumor-infiltrating M2 macrophages. In summary, our results suggest the MARCKS/AXL complex serves as a potential immunotherapeutic target for reprogramming the tumor microenvironment.

<<14>> miR-22 GENE THERAPY TREATS HCC IN MICE

Ying Hu, Farzam Vaziri, Tahereh Setayesh, Yu-Jui Yvonne Wan

Hepatocellular carcinoma (HCC) has become an emerging health burden due to an increase in obesity. With limited therapeutic options available, there is an urgent need to develop alternative treatments for HCC. miR-22 is implicated in the development of various types of cancer including liver and colon among others. Based on the TCGA Data Portal, miR-22 level is inversely associated with the depth of HCC stage, invasion, and overall survival. Thus, miR-22 can be an HCC suppressor. This study examines whether delivery of miR-22 treats orthotopic HCC in immunocompetent mice.

Using the Sleeping Beauty transposon system, HCC mouse models were established by somatic integration of HCC genetic hallmarks of activated AKT and RAS (myr-AKT1 and NRasV12) via hydrodynamic injection. The produced tumor had human HCC features including elevated Galectin 1, Glypican 3, CD133, and α -fetoprotein. AAV8-miR-22 treatment was initiated at 7 days after AKT/RAS delivery, i.e., tumor initiation. At that time, the liver-to-body weight ratio was doubled (8%) compared with healthy livers. The liver-to-body weight ratio of AAV8 control mice reached 28%, whereas the liver-to-body ratio of miR-22-treated mice was 9%. Light microscopy showed that the control livers had multiple, large nodules that occupied greater than 80% of the section, whereas the miR-22-treated livers only had dysplastic foci and vacuolar degeneration. Additionally, HCC development was accompanied by splenomegaly, typically found in patients with HCC, suggesting increased immunological activity and infiltration of foreign cells. Excitingly, miR-22 treatment also reduced the spleen weight. Transcriptome profiling revealed significant up-regulation of IL-6/JAK/STAT3 and IL-17 signaling in HCC, which were both reduced by miR-22 treatment. In consistency, flow cytometry analysis showed increased IL17A⁺ T cells that included both CD4⁻ and CD4⁺ T cells in HCC, which were also reduced by miR-22 treatment.

Together, miR-22 gene therapy treats HCC effectively. It is likely that miR-22, acting via epigenetic modification, reprogram the function of immune cells thereby inhibiting IL-6/JAK/STAT3-IL-17A axis, which are implicated in HCC formation.

<<15>> TARGETING GALECTIN 1 TREATS HEPATOCELLULAR CARCINOMA IN MOUSE MODELS

Tahereh Setayesh¹, Farzam Vaziri¹, Ying Hu¹, Guiyan Yang¹, Karla Damian¹, Ruiwu Liu², Kit S. Lam², Yu-Jui Yvonne Wan¹

¹Department of Pathology and Laboratory Medicine, University of California Davis, Sacramento, CA, USA

²Department of Biochemistry and Molecular Medicine, University of California Davis, Sacramento, CA, USA

Galectin 1 (Gal1) is a carbohydrate-binding lectin. Gal1 is implicated in epithelial-mesenchymal transition. It is also overexpressed in hepatocellular carcinoma (HCC). To goal of this study is to understand the roles of Gal in HCC tumorigenesis and treatment. An orthotopic HCC mouse model was employed by introducing myr-AKT and NRasV12 (AKT/RAS) via hydrodynamic injection to wild-type FVB/N mice. A novel small molecule Gal inhibitor named LLS30 was used to study its effect in HCC treatment. In addition, knockdown and forced expression of Gal1 was done using adeno associated virus serotype 9. The results revealed that Gal1 overexpression reduced the overall survival of HCC bearing mice. In contrast, LLS30 and silencing Gal1 markedly reduced tumor size and improved liver function measured by AST and ALT. Moreover, LLS30 was as effective as lenvatinib, a standard HCC treatment medication, in reducing tumor load. Further, LLS30 reduced the toxicity caused by lenvatinib. Excitingly, gene therapy showed that silencing the Gal1 two days prior to tumor initiation could reduce the liver/body weight ratio by 50%. Moreover, silencing Gal1 one week prior to the anticipated death of HCC-bearing mice reduced the liver/body weight ratio by 30% and prolonged the survival. Taken together, our novel findings show that Gal1 is essential for tumor progression at the early stage of HCC development. In addition, silencing Gal1 at the end of stage of HCC prolongs survival. Thus, targeting Gal 1 is an effective way to treat HCC.

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<<16>> PATIENTS WITH SOFT TISSUE SARCOMAS HARBOR AN INTRATUMORAL MICROBIOME WHICH IS LINKED WITH IMMUNE INFILTRATE AND PROGNOSIS

Lauren M. Perry¹, Sylvia M. Cruz¹, Morgan A. Darrow², Louis B. Jones³, Ugur N. Basmaci¹, Matthew L. Settles⁴, Blythe Durbin-Johnson⁴, Arta M. Monjazebe⁵, Janai Carr-Ascher⁶, Steven W. Thorpe⁷, Sean J. Judge¹, William J. Murphy^{6,8}, Jonathan A. Eisen⁹, Robert J. Canter¹

¹Division of Surgical Oncology, Department of Surgery, University of California Davis, Sacramento, CA, USA

²Department of Pathology and Laboratory Medicine, University of California Davis, Sacramento, CA, USA

³Dallas Sarcoma Associates, Dallas, TX, USA

⁴Department of Bioinformatics, University of California Davis Genome Center, Davis, CA, USA

⁵Department of Radiation Oncology, University of California Davis, Sacramento, CA, USA

⁶Division of Hematology and Oncology, Department of Medicine, University of California Davis, Sacramento, CA, USA

⁷Division of Musculoskeletal Oncology, Department of Orthopedic Surgery, University of California Davis, Sacramento, CA, USA

⁸Department of Dermatology, University of California Davis, Sacramento, CA, USA

⁹Department of Medical Microbiology and Immunology, University of California Davis, Davis, CA, USA

Background: Groundbreaking studies have linked the gut microbiome with anti-tumor immune responses following immunotherapy, and mounting evidence demonstrates the existence of intratumoral microbiomes in solid cancers. Therefore, we sought to characterize the intratumoral and gut microbiome among soft tissue sarcomas (STS) patients undergoing preoperative radiotherapy (RT) before surgery.

Methods: From September 2019 to May 2021, we prospectively obtained tumor and stool samples from adults with non-metastatic STS at image-guided biopsy and surgery using a rigorous sterile collection protocol. Metagenomic classification estimated abundance using the genus and species taxonomic levels, and these data were analyzed with respect to clinicopathologic factors

Results: Over this 20-month period, we enrolled 15 patients; 4 (27%) developed metastases and 3 (20%) died. Despite high human DNA abundance (>99%), we detected a consistent proportion of bacterial DNA (0.02-0.03%) in all tumors. In patients with metastases, *Piscirickettsia* (P=0.002) and *Respirovirus* (P=0.04) were differentially abundant in the pre-RT tumor microbiome. In contrast, the gut microbiome was represented mostly by bacterial DNA (>50%) rather than human DNA (<0.1%). Gut microbiome β -diversity analysis demonstrated no clustering by RT or clinical characteristics. Notably, one patient exhibited markedly greater abundance of intratumoral viral DNA (0.01%) compared to all other samples (0%). Further analysis demonstrated human herpesvirus 6B exclusivity in these tumor samples, with corresponding enrichment of NK cells.

Conclusions: In this prospective analysis with strict sterile procedures, we demonstrate the presence of a measurable intratumoral microbiome in STS patients with clinical relevance. Further studies are warranted to confirm the significance of these findings.

<<17>> EFFICACY AND SAFETY OF BORTEZOMIB IN ONCE WEEKLY VS. TWICE WEEKLY DOSING IN THE TREATMENT OF MULTIPLE MYELOMA

Kwan-Keat Ang, Ryan Beechinor (UC Davis Comprehensive Cancer Center)

Michelle Alyssa Quan (UC Davis Internal Medicine)

Aaron Seth Rosenberg (UC Davis Division of Hematology/Oncology)

Introduction: Lenalidomide, bortezomib, and dexamethasone (RVD) is the standard of care induction therapy for multiple myeloma (MM). Twice weekly (BIW) bortezomib is better described than weekly (QW) dosing but may have unacceptable peripheral neuropathy (PN) rates. We compared the safety and efficacy of twice weekly bortezomib versus once weekly.

Methods: A retrospective chart review was performed of patients >18 years old with newly diagnosed MM who received at least 2 cycles RVD induction treatment from July 2014 to July 2020. The primary efficacy outcomes were overall response rate (ORR) and rates of very good partial response or better (\geq VGPR). Secondary outcomes include progression free survival (PFS), rates and grades of PN and dose reductions due to PN.

Results: Twenty-seven patients were identified, 11 QW and 16 BIW. Baseline characteristics were similar in the two groups. Stem cell transplant was utilized in 16 (59%) patients: 6 (54%) in QW and 10 (63%) in BIW groups. ORR was 100% in both groups. VGPR or better was achieved in 82% and 71% in QW and BIW respectively (p=0.7). Median PFS was not reached in either group; Two year PFS in QW was 61% versus 64% in BIW (p = 0.7). All grade PN was reported in 45% of OWB compared to 69% in TWB patients, resulting in PN related dose reductions in 9% vs 44% of patients respectively (P=0.09).

Conclusion: In RVD induction, weekly bortezomib has similar efficacy to twice weekly, with numerically lower incidence of all grade PN and dose-reductions.

<<18>> PERIPHERAL BLOOD TRANSCRIPT SIGNATURES AFTER INTERNAL 131I-mIBG THERAPY IN RELAPSED AND REFRACTORY NEUROBLASTOMA PATIENTS IDENTIFIES EARLY AND LATE BIOMARKERS OF INTERNAL 131I EXPOSURES

Angela C. Evans^{1,2}, *Tim Setzkorn*³, *David A. Edmondson*⁴, *Haley Segelke*², *Paul F. Wilson*¹, *Katherine K. Matthey*⁵, *M. Meaghan Granger*⁶, *Araz Marachelian*⁷, *Daphne A. Haas-Kogan*⁸, *Steven G. DuBois*⁹, *Matthew A. Coleman*^{1,2}

¹*Department of Radiation Oncology, University of California Davis, Sacramento, CA.*

²*Lawrence Livermore National Laboratory, Livermore, CA*

³*Technical University of Munich, School of Medicine, Germany.*

⁴*Cincinnati Children's Hospital Medical Center, Cincinnati OH*

⁵*Department of Pediatrics, University of California San Francisco School of Medicine, San Francisco CA.*

⁶*Department of Pediatrics, Cook Children's Hospital, Fort Worth, TX.*

⁷*Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, CA*

⁸*Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA*

⁹*Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

131I-metaiodobenzylguanidine (131I-mIBG) is a targeted radiation therapy developed for the treatment of advanced neuroblastoma. We have previously shown that this patient cohort can be used to predict absorbed dose associated with early 131I exposure, 72 hours after treatment. We now expand these studies to identify gene expression differences associated with 131I-mIBG exposure 15 days after treatment. Total RNA from peripheral blood lymphocytes was isolated from 288 whole blood samples representing 59 relapsed or refractory neuroblastoma patients before and after 131I-mIBG treatment. We found that several transcripts predictive of early exposure returned to baseline levels by day 15, however, selected transcripts did not return to baseline. At 72 hours, all 17 selected pathway-specific transcripts were differentially expressed. Transcripts CDKN1A ($p < 0.000001$), FDXR ($p < 0.000001$), DDB2 ($p < 0.000001$), and BBC3 ($p < 0.000001$) showed the highest up-regulation at 72 hours post-131I-mIBG exposure, with mean log₂ fold changes of 2.55, 2.93, 1.86, and 1.85, respectively. At 15 days post-131I-mIBG, 11 of the 17 selected transcripts were differentially expressed, with XPC, STAT5B, PRKDC, MDM2, POLH, IGF1R, and SGK1 displaying significant up-regulation at 72 hours and significant down-regulation at 15 days. Interestingly, transcripts FDXR ($p = 0.01$), DDB2 ($p = 0.03$), BCL2 ($p = 0.003$), and SESN1 ($p < 0.0003$) maintained differential expression 15 days after 131I-mIBG treatment. Our studies showcase the use of biodosimetry gene expression panels as predictive biomarkers following early (72 hours) and late (15-day) internal 131I exposure. Our findings also demonstrate the utility of our transcript panel to differentiate exposed from non-exposed individuals up to 15 days post-exposure from internal 131I.

<<19>> NOVEL AUTOPHAGY INHIBITOR FOR THE TREATMENT OF PANCREATIC CANCER

Mythili Ramachandran, Zhao Ma, Yuanpei Li
Biochemistry Molecular Medicine, UC Davis Cancer Center

In this study, we develop a novel autophagy inhibitor targeting one of the most aggressive cell populations present in pancreatic tumors, the pancreatic cancer stem cell (CSC). Targeting this population which has the malignant properties of tumorigenesis/tumor recurrence, the ability to differentiate into a heterogeneous tumor cell types and can self-renew is a new strategy to alleviate the current dismal 10% five-year survival rate of pancreatic cancer. Here we characterize an autophagy inhibitor which is a first-in-class nanoparticle comprised of a chloroquine-derived small molecule drug that can self-assemble into a micelle. Due to its favorable pharmacokinetic properties and the CSC reliance on autophagy, our compound is able to selectively target this cell population both in vitro and in vivo. Additionally, the compound has shown synergy with the current standard of care chemotherapeutic, gemcitabine, with an 88.9% reduction in tumor volume in the combination of the two drugs compared to gemcitabine treated alone ($p < 0.0001$) in two separate treatment regimens using a pancreatic PDX mouse model. We further illustrate that the stem cell population is targeted by inhibiting tumorsphere formation in established pancreatic cancer cell lines MIA-PaCa2 and PANC-1 and in pancreatic PDX-derived CSCs in vitro. The drug treatment also promotes a decrease in pluripotency markers, particularly

in Sox2 levels. Finally, the drug is well-tolerated with a maximum tolerated dose above 100 mg/kg in mice and is orally bioavailable.

<<20>> THE FUNCTION OF CIRCADIAN CLOCK REGULATOR REV-ERBA IN ADVANCED PROSTATE CANCER

Yatian Yang¹, Demin Cai¹, Xiong Zhang¹, Eva Corey², Christopher P. Evans³, Hong-Wu Chen¹

¹*Department of Biochemistry and Molecular Medicine, UC Davis, School of Medicine*

²*Department of Urology, University of Washington, Seattle, WA*

³*Department of Urologic Surgery, UC Davis, School of Medicine*

The circadian clock orchestrates daily rhythms in gene expression, cell proliferation, metabolism, and DNA damage response. Disruption of circadian rhythms is strongly implicated in tumor development. The nuclear hormone receptor Rev-erba (encoded by NR1D1) is an essential circadian clock regulator that functions as a transcriptional repressor. Here we report that NR1D1 is overexpressed and amplified in metastatic castration-resistant prostate cancer (CRPC) tumors and that its gene knockdown or the receptor inhibition by an antagonist markedly inhibits the growth and survival of CRPC cells. Treatment of mice carrying PDX xenograft CRPC tumors with the antagonist potently inhibited tumor growth. Our further studies revealed that Rev-erba plays a positive role in activating major tumorigenic programs including Wnt signaling and cancer stem-like features. Moreover, we demonstrate that while its antagonist strongly down-regulated the expression and activities of Wnt signaling, Rev-erba overexpression significantly increased Wnt signaling and stem-like features. Overall, our work reveals an unexpected function of circadian regulator Rev-erba in control of key tumorigenic programs and nominates Rev-erba as a novel therapeutic target for treatment of advanced prostate cancer such as CRPC.

<<21>> NUCLEAR RECEPTOR ROR- γ IS A NOVEL THERAPEUTIC TARGET FOR NEUROENDOCRINE PROSTATE CANCER (NEPC)

Xiong Zhang¹, Yang Yang¹, Eva Corey², and Hong-Wu Chen¹

¹*Department of Biochemistry and Molecular Medicine, UC Davis, School of Medicine, Sacramento, CA*

²*Department of Urology, University of Washington, Seattle, WA*

Neuroendocrine prostate cancer (NEPC) is a highly aggressive form of prostate cancer with a short survival time (typically < 12 months) from detection, arising either de novo or from prostate adenocarcinoma such as castration-resistance prostate cancer (CRPC) that are treated with anti-androgen receptor (AR) signaling therapies (hence treatment-induced NEPC or tNEPC). Tumor cell lineage plasticity such as aberrant transition to NE is now recognized as a major mechanism that confers resistance to most of the current therapies. However, so far only a few drivers and therapeutic targets of NEPC diseases have been identified. We previously identified nuclear receptor ROR- γ as an effective therapeutic target for CRPC. Here, we report that ROR- γ antagonists and its gene knockdown potently inhibited the growth and survival of multiple cell models of de novo NEPC and tNEPC and the expression of NEPC markers (e.g. SYP, CHGA and ENO2) and neural differentiation driver genes (e.g. ASCL1, BRN2 and SOX2). Our RNA-seq gene expression profiling demonstrated that neuroactive ligand-receptor interaction and cAMP signaling pathways are significantly enriched among genes downregulated by the treatments. Furthermore, our experiments showed that the ROR- γ antagonists potently killed tumor organoids derived from NEPC PDXs, and that when administered intraperitoneally, the antagonist displayed a strong anti-tumor activity in a NEPC PDX tumor model. Therefore, our study identified nuclear receptor ROR- γ as a promising, new therapeutic target for NEPC.

<<22>> NATURAL AND SYNTHETIC ROR γ ANTAGONISTS INHIBIT CASTRATION-RESISTANT PROSTATE CANCER CELL GROWTH THROUGH ROR γ -MEDIATED AR SIGNALING

Hongye Zou¹, Yatian Yang¹, Hong-Wu Chen¹

¹*Department of Biochemistry and Molecular Medicine, UC Davis, School of Medicine*

We previously identified nuclear receptor ROR γ as a novel therapeutic target in castration-resistant prostate cancer (CRPC). Synthetic ROR γ antagonists such as XY018 and SR2211 potently inhibit prostate cancer cell proliferation. Interestingly, several natural compounds including ursolic acid and digoxin were identified as ligands for ROR γ . Ursolic acid is a natural pentacyclic triterpenoid found in many fruits and vegetables and has potential antiviral, anti-inflammatory and anti-cancer activity. Digoxin was first isolated from foxglove plant and is frequently used for treatment of heart conditions such as atrial fibrillation and heart failure. Here we showed that ursolic acid displays a strong activity in inhibition of ROR γ -dependent transactivation function in luciferase reporter gene assay, with potency comparable to that of synthetic ROR γ antagonists XY018 and SR2211. We also found that ursolic acid and digoxin strongly inhibit CRPC cell growth. Our further examination demonstrated that, similar to the synthetic ROR γ antagonists, ursolic acid and digoxin down-regulate AR and its variant AR-V7 expressions in prostate cancer cells in a concentration-dependent manner. Together, our study provides for the first-time evidence that natural ROR γ antagonists ursolic acid and digoxin inhibit CRPC cell growth by blocking ROR γ -mediated AR-signaling.

<<23>> TARGETING DNA REPAIR PATHWAYS IN OVARIAN CANCER CELL LINES

Alan G. Raetz¹, Caili Tong¹, Prof. Jeremy Chien¹

¹*UC Davis Medical Center, Dept of Biochemistry & Molecular Medicine*

Ovarian cancer is often fatal because of late diagnosis and the eventual development of resistance to platinum-based chemotherapy. Cancer cells depend on DNA repair pathways to survive, and PARP inhibitors represent a new class of chemotherapy drugs that target DNA repair pathways and are particularly effective in patients with deficiencies in homologous recombination (HR) genes such as BRCA1/2. VCP (Valosin Containing Protein) modulates ER stress response and protein degradation pathways and is an essential gene in ovarian cancer cells. Accordingly, VCP inhibitor CB-5083 is toxic at sub-micromolar concentrations in many ovarian cancer cell lines. Recent evidence indicates that nuclear VCP binds to PARP1 and the DNA repair proteins LIG3, APE1, and XRCC1, components of the base excision repair pathway, and that nuclear VCP activity is essential for cancer cell viability. We performed immunoprecipitation experiments in ovarian cancer cell lines that suggest the association between VCP and APE1 or LIG3 and found that inhibiting base excision repair with the APE1 inhibitor APEi3 had an additive effect with CB-5083 VCP inhibition and first-line chemotherapy drugs, Carboplatin and Paclitaxel in cell proliferation assays. These results suggest that the novel combination of CB-5083 and APEi3 enhances first-line chemotherapy toxicity by specifically targeting base excision repair in cancer cells.

<<24>> DECIPHERING THE CHEMOTACTIC CIRCUIT: TOWARDS UNDERSTANDING HOW RECIPROCAL CONTROL OF RECEPTOR ACTIVITY AND ACTIN ASSEMBLY STATES REGULATES PROCESSING OF SPATIAL GRADIENTS

Kwabena Badu-Nkansah, Sean Collins

Department of Microbiology and Molecular Genetics, University of California Davis

Cell navigation is fundamental to cancer progression. Many molecular drivers of cell migration are potent determinants of cancer pathogenesis during tumor invasion, extravasation, cancer metastasis, immune cell recruitment and more. An essential class of these drivers are signaling mediators of chemotaxis that enable cells to translate external gradients of chemoattractants; and directionally bias polarization of intracellular signaling modules, plasma membrane composition, and multiple cytoskeletal networks. The chemical circuit of chemotaxis is initiated by chemoattractant mediated activation of G protein-coupled receptors (GPCRs) and

links receptor activity to polarized actin network rearrangements that control cell movement. While the occurrence of actin polarization is known, it is not fully clear how receptor activity determines how spatial information is processed through the chemotactic circuit to actin networks. I hypothesize that chemotactic receptors regulate distinct actin assemblies; and that actin networks, in turn, send reciprocal feedback signals to control receptor activity. I propose to combine optogenetic control of chemotactic signaling, a series of recently developed actin biosensors, and proximity proteomics to determine how receptor inputs and feedback regulation coordinate polarized actin networks. Together these approaches will provide fundamental insights into how receptors directly interface with polarized actin networks to efficiently guide cells during chemotaxis.