26th Annual Cancer Research Symposium
14th Annual Spotlight on Junior Investigators

October 8 - 9, 2020

A virtual event: http://ucdavis.health/symposium26

UCDAVIS HEALTH | COMPREHENSIVE CANCER CENTER

From the Director

I am pleased to welcome you to the UC Davis Comprehensive Cancer Center's 26th Annual Symposium. This year, we are concurrently running the Symposium with our popular 14th Annual Spotlight on Junior Investigators.

In its 26th 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. Theresa Keegan; Session II – Spotlight on Junior Investigators, chaired by Dr. Fred 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 allow cancer focused investigators to highlight their innovative science.

The keynote presentation in Session I, *Cancer Health Disparities: Considering Structural Context, and Multilevel Social Determinants of Health,* brings renowned scientist Dr. Scarlett Lin Gomez, an epidemiologist with research interests in the role of social determinants of health, including race/ethnicity, socioeconomic status, gender, immigration status, sociocultural factors, and neighborhood contextual characteristics on health outcomes.

Dr. Eileen Dolan, an internationally recognized expert in pharmacogenomics of anticancer agent toxicity is the Session II keynote speaker with her presentation, *Diversifying and Training the Next Generation of Cancer Researchers.*

The keynote lecture for Session III will be given by Dr. John Carpten from USC, whose primary research goal is to discover molecular alterations in cancer and to translate these findings into new approaches for prevention, diagnosis and treatment. His presentation is entitled *Biological and Genetic Factors Influencing Disparities: A Novel DNA Repair Mechanism Associated with Triple Negative Breast Cancer in African Americans.*

Our final keynote for Friday's Session IV will be given by our very own Dr. Brian Jonas, now a nationally recognized leukemia researcher. He will speak on *Acute Myeloid Leukemia: Off the Boulevard of Broken Dreams and Into the Fast Lane.*

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

Importantly, the 14th Annual Spotlight on Junior Investigators will be held as part of the Symposium. The "spotlight" is on our most promising early stage cancer researchers who represent the pipeline of scientists who will then take our Cancer Center to new heights.

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,

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
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Luis Carvajal-Carmona, PhD
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Co-Leader, Basic/Translational Science Program
Director, Latinos United for Cancer Health Advancement (LUCHA) Initiative
Associate Professor, Department of Biochemistry and Molecular Medicine

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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

Theresa Keegan, PhD
Co-Leader, Population Sciences and Health Disparities Program, UCD Comprehensive Cancer Center
Associate Professor, Division of Hematology and Oncology, Department of Internal 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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AGENDA

26th Annual Cancer Research Symposium and 14th Annual Spotlight on Junior Investigators

Thursday, October 8, 2020

SESSION I: Population Sciences and Health Disparities

Chair: Theresa Keegan, PhD

Time	Title	Presenter	Location
8:00–8:15 am	Introduction and Welcome	**Primo Lara, MD** Director, Comprehensive Cancer Center, University of California, Davis	Rev
8:15-8:45 am	Keynote Presentation: Cancer Health Disparities: Considering Structural Context, and Multilevel Social Determinants of Health	**Scarlett Lin Gomez, MPH, PhD** Professor, Epidemiology & Biostatistics, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco	
8:45-9:00 am	Q&A		
9:00–9:15 am	Gastrointestinal Cancers in Primary Sclerosing Cholangitis	**Christopher L. Bowlus, MD** Lena Valente Professor and Chief, Division of Gastroenterology and Hepatology, University of California, Davis	
9:15-9:20 am	Q&A		
9:20–9:35 am	Genetic Ancestry and Subtype-Specific Breast Cancer Risk in Latin American Women	**Laura Fejerman, PhD** Associate Professor, Division of Epidemiology, Department of Public Health Sciences, School of Medicine; Co-Director, Women's Cancer Care Program; Leader, Latinos United for Cancer Health Advancement (LUCHA) Initiative, Comprehensive Cancer Center, University of California, Davis	
9:35–9:40 am	Q&A		
9:40–9:55 am	A Series of Implementation Strategies to Increase Reach for Tobacco Treatment with Cancer Patients	**Elisa Tong, MD, MA** Associate Professor, Division of General Internal Medicine; Medical Director, Stop Tobacco Program, Comprehensive Cancer Center, University of California, Davis	
9:55–10:00 am	Q&A		
10:00 – 10:15 am	Treatments for Clinically Localized Prostate Cancer: Systematic Review and Evidence Visualization	**Joshua Fenton, MD, MPH** Professor and Co-Vice Chair of Research, Department of Family and Community Medicine, University of California, Davis	
10:15 - 10:20 am	Q&A		
10:20–10:30 am	**Break**		

SESSION II: Spotlight on Junior Investigators *Chair: Frederick Meyers, MD, MACP*			
Time	**Title**	**Presenter**	**Location**
10:30 – 11:00 am	Keynote Presentation: Diversifying and Training the Next Generation of Cancer Researchers	**Eileen Dolan, PhD** Professor of Medicine, Associate Director for Cancer Education; Chair, Committee on Clinical Pharmacology and Pharmacogenomics, Comprehensive Cancer Center, University of Chicago	Rev
11:00 – 11:15 am	Q&A		
11:15 – 11:25 am	The TP53 P72R SNP Alters Allelic Selection and Affects the Behavior of Mutant p53 in Human Cancer	**Cristabelle De Souza, PhD** Department of Biochemistry and Molecular Medicine, UC Davis Medical Center; University of New Mexico Biomedical Sciences Graduate Program	
11:25 – 11:30 am	Q&A		
11:30 – 11:40 am	Modeling Familial Pancreatic Cancer with CRISPR/Cas9 to Develop Personalized Cancer Therapy	**Keely Ji** Department of Microbiology and Molecular Genetics, University of California, Davis	
11:40 – 11:45 am	Q&A		
11:45 – 11:55 am	Ketogenic Diet Mitigates Cachexia in a Pancreatic Ductal Adenocarcinoma Mouse Model	**Natalia E. Cortez** Department of Nutrition, University of California, Davis	
11:55 – 12:00 pm	Q&A		
12:00 – 12:10 pm	**Break**		
12:10 – 12:45 pm	**Poster Sessions**	**Junior Investigators (Blocks A1 – A4)**	Webex
12:50 – 1:25 pm	**Poster Sessions**	**Junior Investigators (Block A5)** **Faculty Investigators (Block B1)**	Webex
1:30 – 1:40 pm	A Novel Approach for Understanding Metastatic Pathways Between Sarcoma Subtypes and Its Potential to Identify New Therapies for Patients	**Maria Muñoz** Division of Hematology Oncology, Department of Internal Medicine, University of California, Davis	Rev
1:40 – 1:45 pm	Q&A		
1:45 – 1:55 pm	Evaluation of Novel Galectin-1 Inhibitors in Pancreatic Cancer	**Brandy A. Weathers** Department of Nutrition, University of California, Davis	
1:55 – 2:00 pm	Q&A		
2:00 – 2:10 pm	The Role of Radiation Therapy in Addition to Lumpectomy and Hormone Therapy in Men 70 Years of Age and Older with Early Breast Cancer: A NCDB Analysis	**Lauren M. Perry, MD** Division of Surgical Oncology, Department of Surgery, University of California, Davis Medical Center	

2:10 – 2:15 pm	Q&A	
2:15 – 2:30 pm	**Break**	

SESSION III: Basic/Translational Science

Chair: Luis Carvajal-Carmona, PhD

Time	Title	Presenter	Location
2:30 – 3:00 pm	Keynote Presentation: Biological and Genetic Factors Influencing Disparities: A Novel DNA Repair Mechanism Associated with Triple Negative Breast Cancer in African Americans	**John D. Carpten, PhD** Professor, Department of Urology; Chair, Department of Translational Genomics; Director, Institute for Translational Genomics; Director, Molecular Genomics Core; Co-Leader, Norris Comprehensive Cancer Center, University of Southern California	Rev
3:00 – 3:15 pm	Q&A		
3:15 – 3:30 pm	Phase 1 Clinical Trial of Inhaled Recombinant Human IL-15 in Dogs with Pulmonary Metastasis	**Robert B. Rebhun, DVM, PhD, DACVIM** (Oncology) Professor and Maxine Adler Endowed Chair in Oncology, School of Veterinary Medicine, University of California, Davis	
3:30 – 3:35 pm	Q&A		
3:35 – 3:50 pm	Translational Immuno-Oncology at UC Davis	**Arta Monir Monjazeb, MD, PhD** Associate Professor of Radiation Oncology CCSG Staff Investigator for Immunotherapy Laboratory of Cancer Immunology, Comprehensive Cancer Center, University of California, Davis	
3:50 – 3:55 pm	Q&A		
3:55 – 4:10 pm	Targeting Immunosuppressive Factor CD47 in Cancer Radiotherapy	**Jian-Jian Li, MD, PhD** Professor Department of Radiation Oncology, School of Medicine University of California, Davis	
4:10 – 4:15 pm	Q&A		
4:15 – 4:30 pm	Translation Initiation and Cancer: Structural Insight into the Mechanism of mRNA Recruitment and Scanning	**Christopher S. Fraser, PhD** Professor, Department of Molecular and Cellular Biology, College of Biological Sciences, University of California, Davis	
4:30 – 4:35 pm	Q&A		
End of Day 1			

Friday, October 9, 2020			
Time	**Title**	**Presenter**	**Location**
8:00 – 8:35 am	**Poster Session**	**Junior Investigators (Blocks C1 – C4)**	Webex
8:40 – 9:15 am	**Poster Session**	**Faculty Investigators (Blocks D1 – D2)**	Webex
9:15 – 9:30 am	**Break**		
SESSION IV: Clinical Research *Chair: Karen Kelly, MD*			
9:30 – 10:00 am	Keynote Presentation: AML: Off the Boulevard of Broken Dreams and Into the Fast Lane	**Brian Jonas, MD, PhD** UC Davis, Associate Professor of Medicine, School of Medicine, University of California, Davis	Rev
10:00 – 10:15 am	Q&A		
10:15 – 10:30 am	Up is Down and Down is Up - Update on Donor Selection and GvHD Prevention Strategies in Allogeneic Stem Cell Transplantation	**Rasmus Hoeg, MD** Assistant Professor of Medicine University of California, Davis	
10:30 – 10:35 am	Q&A		
10:35 – 10:50 am	The UCHMC Multiple Myeloma Working Group: Successes, Setbacks and Future Directions	**Aaron Seth Rosenberg, MD, MS** Assistant Professor of Medicine University of California, Davis	
10:50 – 10:55 am	Q&A		
10:55 – 11:10 am	The Future of Cellular Therapy	**Mehrdad Abedi, MD** Professor of Medicine; Director, Alpha Stem Cell Clinic University of California, Davis	
11:10 – 11:15 am	Q&A		
11:15 – 11:25 am	Closing Remarks and Poster Awards Announcement	**Primo Lara, MD** Director, Comprehensive Cancer Center, University of California, Davis	
Symposium Close			

ORAL PRESENTATIONS

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

Scarlett Lin Gomez, MPH, PhD
Professor, Epidemiology & Biostatistics
Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco

Dr. Scarlett Lin Gomez is an epidemiologist with research interests in the role of social determinants of health, including race/ethnicity, socioeconomic status, gender, immigration status, sociocultural factors, and neighborhood contextual characteristics, on health outcomes. She has a BA in biochemistry from UC Berkeley, an MPH degree in Epidemiology from the University of Michigan, and PhD in Epidemiology from Stanford University. She spent 20 years at the Cancer Prevention Institute of California and is now Professor in the Department of Epidemiology and Biostatistics at UCSF. She is also Director of the Greater Bay Area Cancer Registry, a part of the California Cancer Registry and the NCI Surveillance Epidemiology End Results (SEER) Program. She has contributed surveillance data regarding cancer incidence and outcome patterns and trends for distinct Asian American, Native Hawaiian, and Pacific Islander and Hispanic ethnic groups, as well as cancer patterns by nativity status and neighborhood characteristics. She developed the California Neighborhoods Data System, a compilation of small-area level data on social and built environment characteristics. These neighborhood data have been used in several dozen studies and cohort infrastructures to evaluate the impact of social and built neighborhood environment factors on disease outcomes. She is currently PI or MPI of multiple NIH studies focusing on: lung cancer risk in Asian American female never smokers; disparities in cancer survivorship care; multilevel factors impacting treatment decision making and patient-reported outcomes among diverse prostate cancer patient populations; development of a virtual patient navigation program for Asian American cancer patients; multilevel factors influencing treatment receipt and survival among Asian American women with breast cancer; and multilevel factors influencing racial/ethnic disparities in survival among women with ovarian cancer. She is also a Project Leader of the national RESPOND study of prostate cancer in African American men. Dr. Gomez has served on advisory committees, expert panels, and think tanks that contribute to the national discussion around health disparities.

Eileen Dolan, PhD
Professor of Medicine
Associate Director for Cancer Education
Chair, Committee on Clinical Pharmacology and Pharmacogenomics
University of Chicago Comprehensive Cancer Center

Dr. M. Eileen Dolan is an internationally recognized expert in pharmacogenomics of anticancer agent toxicity. Dr. Dolan earned her PhD from the Purdue University went on to complete a postdoctoral fellowship at Pennsylvania State University School of Medicine. Dr. Dolan accepted her first faculty position in the Department of Medicine at the University of Chicago (UChicago) in 1989 and is currently a tenured Professor of Medicine. She serves in several leadership positions at the UChicago. She is Chair of the Committee on Clinical Pharmacology and Pharmacogenomics which includes a board-certified training program for clinical and post-doctoral fellows. Several fellows under her direction received national, peer-reviewed funding for their research projects and went on to distinguished careers in academic medicine. In addition to training clinical and post-doctoral fellows, she mentored graduate students, medical students, undergraduates, and high school students. Within the UChicago Medicine Comprehensive Cancer Center, she is Associate Director for Education. In this capacity, she initiated a summer research program for underrepresented high school and undergraduate students and high school educators funded through an NCI grant that provides hands-on cancer research experiences for talented college students in Chicago communities and serves as a catalyst for student growth and interest in science careers. She is co-PI of the UChicago Breast Cancer Disparities Program, a graduate program funded by Susan G. Komen that provides support for students interested in Cancer Disparities. As evidence of her education and mentoring, she was recognized as the recipient of the 2016 UChicago Biological Sciences Division (BSD) Distinguished Educator/Mentor Award. She is co-chair the BSD Diversity Committee whose mission is to enhance diversity and inclusion of Biosciences trainees. In terms of research, her laboratory performs clinical genome wide association studies to identify genetic variants associated with chemotherapeutic toxicity, most notably chemotherapy-induced peripheral neuropathy, hearing loss and tinnitus in pediatric and adult cancer patients. Her laboratory developed preclinical models to functionally validate genetic variants using patient derived induced pluripotent stem cells. She has over 275 publications and has given talks at national and international meetings. She has been continuously funded for more than 30 years through the National Institute of Health. She has won several awards including Purdue University Distinguished Women Scholars Award, Purdue University School of Pharmacy Distinguished Alumni Award, University of Dayton Distinguished Alumni Award, American Cancer Society (ACS) Ambassador of Hope, and ACS, IL Presidential Award for Volunteer Contributions to Research.

John D. Carpten, PhD
Professor, Department of Urology
Chair, Department of Translational Genomics
Director, Institute for Translational Genomics
Director, Molecular Genomics Core
Co-Leader, Norris Comprehensive Cancer Center
University of Southern California

Dr. Carpten currently serves as Professor and Chair for the Department of Translational Genomics, and Director of the Institute for Translational Genomics, Keck School of Medicine, University of Southern California, Los Angeles, CA. He received his PhD in Molecular, Cellular and Developmental Biology from the Ohio State University. Prior to his current appointment at USC, he served as Professor and Deputy Director of Basic Sciences at the Translational Genomics Research Institute (TGen), Phoenix, AZ. Dr. Carpten's expertise spans a very broad range of research disciplines including germline genetics, tumor profiling, cancer cell biology, functional genomics, and health disparities. The primary goal of Dr. Carpten's research program is to discover molecular alterations in cancer and to translate these findings into new approaches for prevention, diagnosis and treatment. In support of this goal, his program is actively involved in the development and application of cutting-edge technologies and novel bioinformatics approaches for discovery research. Dr. Carpten has co-authored 190 publications in scientific journals that include Science, Nature, Nature Genetics, Cancer Cell, Cancer Research, Molecular Cancer Therapeutics, and the New England Journal of Medicine. Dr. Carpten has an intense focus on understanding the role of biology in cancer health disparities. Through his leadership, the African American Hereditary Prostate Cancer Study (AAHPC) Network was conceived. This study has become a model for genetic studies in underrepresented populations and led to the first genome wide scan for prostate cancer susceptibility genes in African Americans. His work has impacted our understanding of a variety of cancer types that disproportionately affect racial and ethnic minorities including prostate cancer, breast cancer, colon cancer, brain cancer, multiple myeloma, and pediatric cancers. Dr. Carpten was names a Science Trailblazer by Spectrum Magazine in 2006, and was awarded the AACR and Susan G. Komen Distinguished Lectureship on the Science of Cancer Health Disparities in 2014, and the AACR Jane Cooke Wright Lectureship in 2018 for his untiring work in ensuring that all people are equally represented in science and innovative healthcare. In 2019, he served as Program Committee Chair for the AACR Annual Conference in Atlanta, GA, which included over 21,500 international participants. It is his hope that his efforts will lead to improvements in cancer management and outcomes for all patients.

Brian Jonas, PhD
Associate Professor of Medicine
School of Medicine
University of California, Davis

Dr. Brian Jonas is an Associate Professor in the Division of Hematology and Oncology at UC Davis Comprehensive Cancer Center (UCDCCC), where he specializes in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia(ALL), and other hematologic malignancies. He earned is MD and PhD degrees from UC Davis as part of their Physician-Scientist Training program, and he completed his residency in Internal Medicine and fellowship in Hematology and Oncology at Stanford as part of their ABIM research pathway. His postdoctoral research fellowship was in the laboratory of Dr. Ravindra Majeti at Stanford and focused on acute myeloid leukemia stem cell (LSC) biology, and he was awarded a Leukemia & Lymphoma Society Career Development Award. He also was named a K12 scholar in the NIH/NCI UC Davis Paul Calabresi Clinical Oncology K12 Mentored Clinical Research Program and formed an AML-focused translational research group focused on studying strategies to diagnose, prevent, or overcome therapy resistance. Dr. Jonas leads a thematic clinical and translational research program in AML, MDS, and ALL with an emphasis on biomarker development, early drug development, and leukemia stem cells. He has been awarded intramural and extramural funding to support his research, and he is PI on several open or pending clinical trials, including multiple investigator-initiated trials and two ETCTN trials on which he serves as the national study chair. He chairs the UCDCCC Hematological Malignancies Working Group and is co-chair of the UCDCCC Data and Safety Monitoring Committee. Over the past five years, Dr. Jonas has had the highest accrual to hematological malignancy clinical trials at UC Davis. His latest awards include the 2020 UCD Internal Medicine Outstanding Clinician Award and the NCI Cancer Clinical Investigator Team Leadership Award (CCITLA) for exemplary contributions to clinical trials at the Cancer Center.

ABSTRACTS OF ORAL PRESENTATIONS (THURSDAY)

SESSION I: Populations Sciences and Health Disparities

Chair: Theresa Keegan, PhD

KEYNOTE LECTURE: CANCER HEALTH DISPARITIES: CONSIDERING STRUCTURAL CONTEXT, AND MULTLEVEL SOCIAL DETERMINATS OF HEATLH

Scarlett Lin Gomez, PhD, Professor, Epidemiology & Biostatistics, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco

Structural context and social determinants of health are considered the fundamental causes of health and disease and a primary driver of health disparities. Dr. Gomez will present a conceptual framework for studying multilevel social determinants of health, and the application of this framework through several case studies.

GASTROINTESTINAL CANCERS IN PRIMARY SCLEROSING CHOLANGITIS

Christopher L. Bowlus, MD, Lena Valente Professor and Chief, Division of Gastroenterology and Hepatology, University of California, Davis

Dr. Bowlus will discuss primary sclerosing cholangitis (PSC), a rare inflammatory disease of the biliary tract frequently found in association with inflammatory bowel disease (IBD). PSC affects people of all ages, but the peak incidence is in the 4 decade of life and unlike most autoimmune disorders, men are affected more frequently than women (3:2). Stricturing of the bile ducts leads to cholestasis, biliary cirrhosis, and ultimately liver failure with a median time from diagnosis to death or liver transplantation of 20 years. In addition, to progression to cirrhosis, patients with PSC are at high risk of developing hepatobiliary (HB) cancers, primarily cholangiocarcinoma, but also gallbladder cancer and hepatocellular carcinoma. The incidence of cholangiocarcinoma is ~1 per 100 patient-years with the highest incidence in the first year following diagnosis. Older age at diagnosis, male sex, and the presence of IBD have been identified as risk factors for HB cancers. Diagnosis of pre-malignant or early stages of HB cancer allow for successful treatment including liver transplantation, but surveillance methods have poor sensitivity and lack objective data to support their efficacy. Further, PSC patients with IBD are at risk of colon cancer several times greater than the general population and greater than IBD patients without PSC.

GENETIC ANCESTRY AND SUBTYPE-SPECIFIC BREAST CANCER RISK IN LATIN AMERICAN WOMEN

Laura Fejerman, PhD, Associate Professor, Division of Epidemiology, Department of Public Health Sciences, School of Medicine; Co-Director, Women's Cancer Care Program; Leader, Latinos United for Cancer Health Advancement (LUCHA) Initiative, Comprehensive Cancer Center, University of California, Davis

Dr. Fejerman's research focuses on the discovery of genetic and non-genetic factors that contribute to breast cancer risk and prognosis in Latinas. Her past work established a relationship between genetic ancestry and breast cancer risk, where higher European ancestry in U.S. and Mexican Latinas was associated with an increased risk. Her subsequent research has built upon this observation, discovering risk associated genetic variants through admixture mapping and genome-wide association approaches. Common variants within the 6q25 chromosomal region (which harbors the Estrogen Receptor 1 gene) show subtype-specific associations, which need to be further explored. Understanding the functional implications of these variants could provide insights for cancer prevention.

A SERIES OF IMPLEMENTATION STRATEGIES TO INCREASE REACH FOR TOBACCO TREATMENT WITH CANCER PATIENTS

Elisa Tong, MD, MA, Associate Professor, Division of General Internal Medicine; Medical Director, Stop Tobacco Program, Comprehensive Cancer Center, University of California, Davis

The University of California Davis Comprehensive Cancer Center (UCDCCC) was selected to join the National Cancer Institute Cancer Center Cessation Initiative (NCI C3I) to integrate tobacco treatment with cancer care. Dr. Tong will present the findings from the study implementation strategies, including initiating cancer provider and staff education and training (Strategy #1), the Ask-Advise-Connect workflow with medical assistants assessing and referring within the clinic encounter (Strategy #2), and Closing Care Gaps outreach to contact "unassisted" smokers outside of the clinic encounter (Strategy #3). Over the two-year study period, tobacco assessment rates improved from 84% to 96%. Tobacco treatment reach for patients increased from a baseline of <10% to 31% with Strategy #2 (Ask-Advise-Connect) to 41% by adding Strategy #3 (Closing Care Gaps); overall 62% of patients were at least advised to quit. Tobacco treatment program orders and outreach improved by 6-fold. For tobacco treatment program Effectiveness, among 118 patients who engaged in treatment, past-week abstinence at 6 months was 22.9% (missing data assumed to be smoking). Adoption and implementation of tobacco treatment program annual referrals (Strategy #2) were highest in medical (5-10 fold) and surgical oncology (3-fold); radiation oncology referrals remained low due to a different clinic workflow and electronic health record module. The series of implementation strategies rapidly improved tobacco treatment reach among the UCDCCC patients who use tobacco, with quit rates similar to existing literature. Refinements and sustainability efforts with Health Management Education are underway to continue the goal of consistently offering tobacco treatment to all identified cancer patients.

TREATMENTS FOR CLINICALLY LOCALIZED PROSTATE CANCER: SYSTEMATIC REVIEW AND EVIDENCE VISUALIZATION

Joshua Fenton, MD, MPH, Professor and Co-Vice Chair of Research, Department of Family and Community Medicine, University of California, Davis

To inform the 2018 U.S. Preventive Services Task Force prostate cancer screening recommendation, Dr. Fenton led systematic reviews of the benefits and harms of prostate cancer screening and treatment. He will briefly review evidence related to localized prostate cancer treatment and how this evidence influenced the Task Force final recommendation. Subsequently, Dr. Fenton will describe a Patient Centered Outcome Research Institute initiative to improve the accessibility, flexibility, and timeliness of systematic reviews using evidence visualization. He will demonstrate new evidence visualizations created for clinicians and patients to compare the effectiveness and harms of alternative treatments for localized prostate cancer.

SESSION II: Spotlight on Junior Investigators

Chair: Frederick Meyers, MD, MACP

KEYNOTE LECTURE: DIVERSIFYING AND TRAINING THE NEXT GENERATION OF CANCER RESEARCHERS

Eileen Dolan, MD, Professor of Medicine; Associate Director for Cancer Education; Chair, Committee on Clinical Pharmacology and Pharmacogenomics, Comprehensive Cancer Center, University of Chicago

One of the central missions of the University of Chicago Medicine Comprehensive Cancer Center (UCCCC) is to diversify and train the next generation of cancer researchers and physicians and to support the career development of aspiring and experienced cancer professionals. This is accomplished through integrating and developing programming and activities to maximize their impact and leverage existing infrastructure and resources. The UCCCC has invested significant resources into 1) integrating institutional cancer-focused training activities at all levels; 2) developing new pipeline programs for high school, college students and high school educators interested in cancer research careers; 3) enhancing multidisciplinary, specialized training opportunities for graduate students; 4) focusing career enhancement activities on improving diversity and supporting an inclusive environment in the cancer research and care workforce; and 5) broadening the professional development opportunities for senior fellows and faculty. In this presentation, I will discuss current programs to improve diversity in the workforce, support an inclusive environment and train the next generation of cancer researchers.

THE TP53 P72R SNP ALTERS ALLELIC SELECTION AND AFFECTS THE BEHAVIOR OF MUTAN p53 IN HUMAN CANCER

Cristabelle De Souza, PhD [1,2], Jill Madden, PhD[3], Devin C. Koestler, PhD[4], Dennis Minn, BS[5], Alan G. Raetz, PhD[1], Zheng Zhu, MD, PhD[1], Wen-wu Xiao, MD, PhD[1], Neeki Tahmassebi, BS[1], Harikumara Reddy, BS[1], Nina Nelson, BS[1], Anthony N. Karnezis, MD, PhD[6], Jeremy Chien, PhD[1,7]

[1]Department of Biochemistry and Molecular Medicine, UC Davis Medical Center, Sacramento, CA; [2]University of New Mexico Biomedical Sciences Graduate Program, Albuquerque, NM; [3]The Manton Center for Orphan Disease Research and The Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA; [4]Department of Biostatistics and Data Science, Kansas University Medical Center, Kansas City, KS; [5]College of Information and Computer Sciences, University of Massachusetts, Amherst, MA; [6]Department of Pathology and Laboratory Medicine, UC Davis Medical Center, Sacramento, CA; [7]Department of Obstetrics and Gynecology, UC Davis Medical Center, Sacramento, CA

Background: TP53 mutations are present in more than 50% of human cancers. The purpose of this study was to determine the effect of the intragenic P72R SNP (rs1042522) on the oncogenic properties of mutant p53 in cancer.

Methods: The P72R allelic selection in tumor samples was determined from the genotype calls and a Gaussian distributed mixture model. The effect of the P72R SNP on mutant p53 was determined in two cancer cell lines and a xenograft model. RNA-sequencing, Chromatin-Immunoprecipitation and Immunoblotting were performed to describe the mechanistic effects of the P72R SNP on p53 transcriptional targets.

Results: We identified 409 patients with somatic mutations in TP53 on a heterozygous P72R germline background. We observed a significant selection bias for the R72 SNP in mutant TP53 allele from the genotype calls ($\chi 2$ $P < 5.5*10-8$) and in a Gaussian distributed mixture model ($P = 3.3*10-8$). The exogenous expression of three hotspot TP53 mutants with either P72 or R72 SNP in cancer cells indicates the P72 SNP is negatively selected. Finally, p53 mutants with the P72 SNP bind to canonical p53 targets inducing expression of these genes.

Conclusion: This is the largest study to date that demonstrates a selection against the P72 SNP. Our study demonstrates that p53 missense mutants with the P72 SNP partially retain wildtype tumor-suppressive functions, which may explain the selection bias against P72 SNP across cancer types. Our study describes a previously unknown role through which the rs1042522 SNP modifies tumor suppressor activities of mutant p53 in patients.

MODELING FAMILIAL PANCREATIC CANCER WITH CRISPR/Cas9 TO DEVELOP PERSONALIZED CANCER THERAPY

Keely Ji, Eunjung Lee, Qi Tian, Hsien Yi Yang, Pauline Trinh, Chang-il Hwang

Department of Microbiology and Molecular Genetics, University of California, Davis

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States, with a 5-year survival rate of 9%. Despite this alarming rate, there are limitations in the diagnosis and effective treatments available due to drug resistance and cancer heterogeneity. Although the cause of pancreatic cancer is unclear, around 10% of pancreatic cancer is hereditary and is categorized as familial pancreatic cancer (FPC). FPC is associated with germline mutations in genes related to DNA repair processes like that of homologous recombination (HR) and mismatch repair (MMR) pathways. It has been shown that *BRCA1/2* deficient breast and ovarian cancers are sensitive to poly (ADP-ribose) polymerase inhibitor (PARPi) due to the synthetic lethal relationship that PARP has with HR pathway. Furthermore, the recent POLO clinical trial found that PARPi is effective as maintenance therapy for *BRCA1/2* deficient pancreatic cancer patients. Likewise, there is a need to investigate other gene mutations associated with FPC. In this study, we aim to model the gene mutations commonly found in FPC patients using CRISPR/Cas9 technology and assess the efficacy of drugs on these models. As a proof-of-concept, we showed that *Brca2* or *Palb2* deficiency in murine KPC cell line confers the increased sensitivity to PARPi. In addition, it has been shown that epigenetic alterations are crucial components in DNA repair processes. **Therefore, we hypothesize that deficiencies in DNA repair processes will create new epigenetic vulnerabilities that could be targeted in therapy.** To address this *in vitro*, we lentivirally introduced FPC gene-specific gRNA into Cas9 expressing murine *Kras* and *p53* mutant (KPC) mT3-2D cell line. Then, we evaluated the efficiency of gene editing made by Cas9 with the Surveyor assay. Following the confirmation, we established clonally derived cell lines of each FPC gene mutant and confirmed the desired mutations with Sanger sequencing and Inference of CRISPR Edits (ICE) analysis. The efficacy of epigenetic drugs, including bromodomain inhibitors, and quantification of cell viability with alamarBlue assay, was assessed for each FPC mutant clone. We observed that deficiency in HR or MMR pathways conferred sensitivity to bromodomain inhibitors JQ1, Birabresib, and Molibresib. *Atm*, *Bub1b*, *Fancc*, *Mlh1*, and *Msh4* deficient cells were especially sensitive to JQ1. To investigate the mechanism of JQ1 drug sensitivity, we performed RNA-seq with JQ1 treated FPC gene knockout (KO) cells. Principle component analysis (PCA) showed that JQ1 treatment induced changes in the gene expression profile of the cells. Furthermore, gene set enrichment analysis (GSEA) revealed that JQ1 treatment significantly downregulated DNA repair pathways in FPC gene KO cells compared to the Rosa26 KO control. Taken together, these findings support the hypothesis and show that DNA repair deficiency found in FPC can cause sensitivity to bromodomain inhibitors. This conclusion lays the ground to assess the efficacy of bromodomain inhibitor JQ1 in treating FPC *in vivo*, which would help pave the road in developing personalized cancer therapy for FPC.

Acknowledgement: KJ is supported by the UC Davis CBS Dean's Circle Summer Undergraduate Research Program. KJ is a participant in the UC Davis Maximizing Access to Research Careers (MARC) Program (NIGMS-MARC-U-STAR grant GM083894).

KETOGENIC DIET MITIGATES CACHEXIA IN A PANCREATIC DUCTAL ADENOCARCINOMA MOUSE MODEL

Natalia E. Cortez, Brian V. Hong, Emily M. Villarreal, Gerardo G. Mackenzie

Department of Nutrition, University of California, Davis

Background: Cancer cachexia is a multifactorial disorder characterized by involuntary and ongoing wasting of skeletal muscle. More than 80% of patients with pancreatic ductal adenocarcinoma (PDA) present with cachexia and up to 20% die directly from it. Previous studies have shown that the ketogenic diet (KD) has anti-tumor potential, and suggest that it could be an effective adjuvant therapy for PDA and its corresponding cachexia. However, studies with models that closely recapitulate human PDA are needed. Additionally, the effects and mechanisms of action of a KD on PDA-associated cachexia and tumor growth are unknown.

Objective: To determine whether a KD plus chemotherapy mitigates cachexia and/or increases survival in a clinically relevant genetically engineered LSL-KrasG12D/+; LSL-Trp53R172H/+; Pdx1-Cre (KPC) model of PDA.

Methods: After confirming the presence of a pancreatic tumor by high resolution ultrasound imaging, male and female KPC mice were fed either a control diet (CD; %kcal: 14% protein, 70% carb, 16% fat), or a KD (%kcal: 14% protein, <1% carb, 85% fat). The effect of each dietary group was evaluated alone and in combination with gemcitabine, a chemotherapy drug. Forelimb grip strength, body composition, and non-fasting glucose and ketone levels were evaluated at baseline, monthly and at time of sacrifice. Mice were euthanized and organs harvested when an endpoint related to PDA was met.

Results: Throughout the study, blood ketones were significantly elevated in KD mice compared to control mice. The mean survival times among groups were 61, 67, 85, and 96 days for CD, KD, CD + Gemcitabine, and KD + Gemcitabine, respectively. KPC mice fed a KD plus gemcitabine exhibited a significant increase in median survival when compared to those fed CD alone. KPC mice fed CD, either alone or in combination with chemotherapy, showed a time-dependent decline in muscle strength by 2 months of intervention. In contrast, KPC mice fed a KD, either alone or combined with chemotherapy, significantly maintained muscle strength after 2 months. Consistent with the preserved motor function, when evaluating organ weights at time of euthanasia, the mass of the gastrocnemius was higher in mice fed a KD compared to those in the CD groups. Moreover, phosphorylated levels of S6 ribosomal protein (p-S6), a downstream target of mTOR that plays a critical role in cachexia, were higher in the gastrocnemius isolated from KPC mice fed a KD than in those CD-fed. Furthermore, KD decreased TNF-α and IFN-γ levels, two cytokines that are implicated in cachexia progression, by 33% and 70% respectively.

Conclusions: Our preliminary findings indicate that KD maximizes and preserves motor function strength during PDA progression. Additional studies are underway to continue to evaluate the mechanisms of how KD improves and preserves muscle strength in PDA.

Research Support: Startup funds and a University of California Comprehensive Cancer Center award to GGM. NEC is supported with a fellowship from UC-MEXU

A NOVEL APPROACH FOR UNDERSTANDING METASTATIC PATHWAYS BETWEEN SARCOMA SUBTYPES AND ITS POTENTIAL TO IDENTIFY NEW THERAPIES FOR PATIENTS

Maria Muñoz, Janai R Carr-Ascher

Division of Hematology Oncology, Department of Internal Medicine, University of California, Davis

This year, an estimated 13,000 people will be diagnosed with soft tissue sarcoma. About 64.7% of patients will survive following diagnosis, but only 15.4% will survive over 5 years if the cancer metastasizes. This uncommon cancer arises from mesenchymal stem cells, and encompasses distinct subtypes including:

Undifferentiated Pleomorphic Sarcoma, Rhabdomyosarcoma, and Leiomyosarcoma. While each subtype is characterized by different histologies and genetic profiles, all are capable of metastasizing to the lungs. Unfortunately, low incidence rates and lack of models makes this a difficult cancer to treat. Our goals are to develop a metastasis model of sarcoma and make comparisons between the primary and metastatic tumor. In doing so, we can characterize the different subtypes of sarcoma and better understand their metastatic pathways. Once identified, we can assume that primary tumor cells with similar pathways will have metastatic potential. Such cells can be targeted early, to prevent future lung metastasis. This will lead to improved treatments for sarcoma patients. To develop the model, we injected mice with GFP-Luciferase tagged tumor cells to verify that they can give rise to metastasis. Cells later expressing GFP-Luciferase in the lungs will be a positive indicator. After collecting tissue, we will enrich for human cells in the primary and metastatic tumor using magnetic beads. Magnetic beads deplete mouse cells from samples and are crucial for the analysis of these tumors. They ensure we solely analyze the human cell population from which the tumors originated. So far, our flow cytometry data has verified that this method effectively enriches for human cells in both tissues. These isolated human cells will provide insight into over- and under-expressed genes among subtypes and between primary and metastatic cells. Analysis can be done via RNA-, exome, ATAC- or HiC sequencing. This will characterize the different subtypes of sarcoma and help distinguish between metastatic and non-metastatic cells. Overall, the development of a metastasis model and comparison among primary and metastatic tumor cells, will advance our understanding of sarcoma and its metastatic pathways which will lead to new treatments for patients.

Acknowledgments: This project was funded by NCI P30CA093373, UC Davis Comprehensive Cancer Center Support Grant (CCSG). All flow-cytometry experiments were conducted at the flow-cytometry core at UC Davis Health which is funded by NCI P30CA093373.

I would also like to thank Dr. Janai R Carr-Ascher for her contributions and guidance with this project.

EVALUATION OF NOVEL GALECTIN-1 INHIBITORS IN PANCREATIC CANCER

Brandy A. Weathers[1], Joanna Wirkus[1], Ran Wei[1], Kit S. Lam[2], Ruiwu Liu[2], Gerardo G. Mackenzie[1]

[1]Department of Nutrition, [2]Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis

Background: Pancreatic cancer is expected to affect over 57,600 people by the year 2020. It is a deadly disease with a mortality rate of 81% and is the ninth most commonly diagnosed cancer in the US. Given that current treatment options are limited and many chemotherapeutic agents do not improve the patient's lifespan, new molecular targets and treatments are needed. Galectin-1 promotes pancreatic carcinogenesis and is a key factor of cancer progression through proliferation, angiogenesis, desmoplasia, and immune evasion. Thus, galectin-1 may represent a potential novel target for treatment.

Objective: To evaluate the efficacy and selectivity of three novel galectin-1 inhibitors (S-LLS30, S-LLS131 and S-LLS132S; all being S-enantiomers of each LLS inhibitor) in multiple human pancreatic cancer cell lines, as well as human lung and colon cancer cell lines.

Methods: Human pancreatic (MIA PaCa-2, Panc-1 and BxPC-3), lung (A549, HT1975 and H358), and colon (HT29, HCT15 and SW480) cell lines were obtained from American Type Culture Collection (Manassas, VA) and were grown in the specific medium and conditions suggested by ATCC. Multiple novel galectin-1 inhibitors (S-LLS30, S-LLS131 and S-LLS132) were tested in a panel of human pancreatic, lung and colon cells in culture, to evaluate their efficacy in cancer cell growth inhibition. Cell growth was determined after 72-hour treatment with each compound. We also compared the efficacy of the novel agents against the human pancreatic normal epithelial cell line, hTERT-HPNE.

Results: All three novel compounds inhibited the growth of human lung, colon, and pancreatic cancer cell lines with micromolar potency. Among the multiple agents, S-LLS132 had the highest potency, inhibiting the growth of all three human pancreatic cancer cell lines in a concentration- and time-dependent manner. At S-LLS132

concentrations of 1.25μM and 2.5μM, there was over 75% growth inhibition in all three of these cell lines (MIA PaCa-2, Panc-1 and BxPC-3). We also evaluated whether S-LLS132 could inhibit the growth of human pancreatic normal epithelial cells. Treatment with S-LLS132 did not significantly reduce HPNE cell growth up to concentrations of 2.5 μM S-LLS132. Compared to the control, 90% of HPNE cells treated with S-LLS132 were viable after 72 h of treatment. Of note, treatment of S-LLS132 for 72 h reduced the growth of MIA PaCa-2 and Panc-1 cells by 98, and 89 %, respectively. These results show that S-LLS132 is selective to pancreatic cancer cells, sparing the normal cells.

Conclusion: Taken together, our preliminary studies indicate that S-LLS132 was the most potent of the galectin-1 inhibitors, strongly reducing cancer cell growth and sparing the normal cells. Current plans include the evaluation of the efficacy of S-LLS132 in pancreatic cancer animal models; assess its mechanism of action and the combination potential of this inhibitor with chemotherapeutic drugs currently in use to treat pancreatic cancer.

Funding: UCDCCC pilot award to GGM and RL. BAW is a PREP Scholar.

THE ROLE OF RADIATION THERAPY IN ADDITION TO LUMPECTOMY AND HORMONE THERAPY IN MEN 70 YEARS OF AGE AND OLDER WITH EARLY BREAST CANCER: A NCDB ANALYSIS

Lauren M. Perry, MD[1], Sarah B. Bateni, MD[1]*, Xiao Zhao, MD[2], Mili Arora, MD[3], Megan E. Daly, MD[2], Susan L. Stewart, PhD[4], Richard J. Bold, MD[1], Robert J. Canter, MD[1], Candice A. M. Sauder, MD[1]*

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**Lauren M. Perry and Sarah B. Bateni contributed equally to this work*

Purpose: Current treatment guidelines for male breast cancer are guided by female-only trials despite data suggesting distinct clinicopathologic differences between sexes. We sought to evaluate if radiation therapy (RT) after lumpectomy was associated with equivalent survival among men ≥ 70 years of age with stage I, estrogen receptor (ER) positive tumors, as seen in women from the Cancer and Leukemia Group B (CALGB) 9343 trial.

Methods: We performed a retrospective analysis of 752 stage I, ER-positive male breast cancer patients ≥70 years who were treated with hormone therapy and surgery, with or without RT, from the National Cancer Database between 2004-2014. Patients were categorized based on surgery and RT (lumpectomy alone, lumpectomy with RT, and mastectomy alone). Multivariable Cox proportional hazards regression analysis was used to compare overall survival between treatment groups.

Results: Most patients underwent total mastectomy, with only 32.6% treated with lumpectomy. Of those who underwent lumpectomy, 72.7% received adjuvant RT. In multivariate analysis, there was no statistical difference in overall survival when comparing lumpectomy alone to lumpectomy with RT (aHR 0.72 [95%CI 0.38-1.37], p=0.31), or when comparing lumpectomy (alone or with RT) and mastectomy (aHR 1.28 [95%CI 0.88-1.87], p=0.20).

Conclusions: In this national sample of elderly men with ER-positive early-stage disease treated with endocrine therapy, there were no significant differences in overall survival when comparing lumpectomy alone to lumpectomy with RT, or lumpectomy (alone or with RT) to mastectomy. These results suggest that less aggressive treatment may be appropriate for a subset of male breast cancer patients.

SESSION III: Basic/Translational Science

Chair: Luis Carvajal-Carmona, PhD

KEYNOTE LECTURE: BIOLOGICAL AND GENETIC FACTORS INFLUENCING DISPARITIES: A NOVEL DNA REPAIR MECHANISM ASSOCIATED WITH TRIPLE NEGATIVE BREAST CANCER IN AFRICAN AMERICANS

John D. Carpten, PhD, Professor, Department of Urology; Chair, Department of Translational Genomics; Director, Institute for Translational Genomics; Director, Molecular Genomics Core; Co-Leader, Norris Comprehensive Cancer Center, University of Southern California

The ability to rapidly sequence the tumor and germline DNA and RNA of an individual using Next Generation Sequencing technologies and bioinformatics holds the eventual promise of revolutionizing our ability to match targeted therapies to tumors harboring biologically associated genetic biomarkers. Although numerous groups are implementing these approaches in treatment selection for cancer patients, aspects related to population heterogeneity remains a confounder and limit the most optimized and appropriate approach. This is particularly important as many tumor types disproportionately affect individuals from underrepresented populations. Our group performed a comprehensive molecular profiling study of patient with metastatic Triple Negative Breast Cancer (TNBC) to identify therapeutically actionable events. From these data we identified somatic alterations at the CTNNA1 locus in African American TNBC. We have performed functional and translational studies demonstrating that inactivating events at the CTNNA1 locus are enriched in TNBC and associated with race. CTNNA1 encodes alpha E-catenin, and we further show that loss of alpha catenin is associated with poor survival in an independent cohort. Moreover, we have identified a novel nuclear role for alpha catenin in DNA repair, where loss of alpha catenin confers chemo resistance, while also sensitizing cells to G2M checkpoint inhibitors. Optimizing Precision Medicine through improving diversity in cohorts might lead to novel insights towards creating more tailored approaches for cancer prognosis and treatment for all patients.

PHASE 1 CLINICAL TRIAL OF INHALED RECOMBINANT HUMAN IL-15 IN DOGS WITH PULMONARY METASTASIS

Rebhun RB[1], York D[1], Judge SJ[2], Brady RV[1], Johnson EG[1], Wittenburg LA[1], Willcox JL[1], Burton JH[1], Al-Nadaf S[1], Skorupski KA[1], Gingrich AA[2,3], Brown CT[3], Woolard KD[4], Culp WTN[1], Monjazeb AM[5], Kent MS[1], Sparger EE[6], Murphy WJ[7], Canter RJ[2].*

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Purpose: We set out to perform a phase 1 clinical trial of inhaled recombinant human IL-15 (rhIL-15) in canine patients with pulmonary metastasis.

Experimental Design: A first-in-dog outpatient phase 1 dose escalation trial of inhaled rhIL-15 is underway in client-owned dogs with naturally occurring pulmonary metastasis secondary to osteosarcoma or melanoma. Inhalation therapy consists of twice daily inhalation of rhIL-15 for 14 days. Clinical responses are being assessed using modified immune RECIST. Pharmacokinetics of rhIL-15 and immune biomarkers are also being evaluated.

Results: Eighteen dogs have been treated at 5 dose levels, ranging from 10 mcg to 70 mcg. Two dose limiting toxicities possibly related to disease have been identified including a single Grade 3 elevation in alanine aminotransferase in the 10 mcg cohort and a Grade 3 abscess formation in 1 dog treated in the 70 mcg cohort. To date, 4 out of 16 evaluable dogs demonstrated clinical benefit from treatment (1 CR, 1 PR, and 2 SD). Two of these dogs exhibited durable responses greater than 6 months after receiving only a single 14-day cycle.

Conclusions: The maximum tolerated dose has not yet been defined. Inhaled rhIL-15 is well tolerated in the dog and shows clinical activity. Preliminary results are encouraging and may support additional trials incorporating inhaled rhIL-15 in combination therapies.

Acknowledgements: Funding for this project was provided by the National Cancer Institute, U01CA224166-01

TRANSLATIONAL IMMUNO-ONCOLOGY AT UC DAVIS

Arta Monir Monjazeb, MD, PhD
Associate Professor of Radiation Oncology
CCSG Staff Investigator for Immunotherapy
Laboratory of Cancer Immunology, Comprehensive Cancer Center, University of California, Davis

Using the unique resources at UC Davis for multi-species comparisons we have developed a novel pipeline for preclinical investigation and clinical translation of novel approaches and concepts in cancer immunotherapy. These studies have resulted in a better understanding of cancer immunology and are directly impacting the clinical care of cancer patients. Several examples from ongoing work at UC Davis will be presented.

TARGETING IMMUNOSUPPRESSIVE FACTOR CD47 IN CANCER RADIOTHERAPY

Jian-Jian Li, MD, PhD
Professor, Department of Radiation Oncology, School of Medicine, University of California, Davis

Accumulating clinical trials have demonstrated a latent efficacy cancer control by combined modality of radiotherapy (RT) with targeted immunotherapy. However, the immunosuppressive factors induced by radiation which may severely compromise the efficacy of immunotherapy are to be identified. This collaborative study at UCDCC demonstrates that immunosuppressive factor CD47, a critical cell surface receptor protecting tumor cells against immune cell attach, can be induced in an array of breast cancer (BC) cells including triple negative subtype. CD47 is found to be concurrently upregulated with HER2 in the radioresistant BC cells and in RT-treated syngeneic mouse breast tumors. Co-expression of CD47 and HER2 is frequently detected in recurrent BC patients with poor prognosis. Animal model of dual antibody treatment elevates BC radiosensitivity and increases tumor inhibition. Thus, these results demonstrate that the two cell surface receptors, CD47 and HER2, can coordinatively contribute to the aggressive growth of resistant BC cells, and immunotherapy targeting both of CD47 and HER2 is suggested in treatment of recurrent BC.

Grant Support: This work was partially supported by National Cancer Institute Grant RO1 CA213830 and a bridging fund from UC Davis Comprehensive Cancer Center.

TRANSLATION INITIATION AND CANCER: STRUCTURAL INSIGHT INTO THE MECHANISM OF mRNA RECRUITMENT AND SCANNING

Christopher S. Fraser, PhD
Professor, Department of Molecular and Cellular Biology, College of Biological Sciences, University of California, Davis

Elevated protein synthesis is a feature of many cancer cells. This can be an outcome of increased signaling to the eukaryotic initiation factor 4F (eIF4F) complex, which is a key regulator of mRNA recruitment to the small ribosomal subunit. Increasing efforts are being made to target this complex with chemotherapeutic agents to specifically inhibit the translation of growth promoting mRNAs. To obtain a more complete picture of how eIF4F controls mRNA recruitment and scanning, we have used cryo-electron microscopy to determine the structure of a reconstituted human 48S complex. The structure reveals insights into early events of translation initiation complex assembly, as well as how eIF4F interacts with subunits of eIF3 near the mRNA exit channel in the 43S complex. The location of eIF4F is consistent with a slotting model of mRNA recruitment and suggests that downstream mRNA is unwound at least in part by being "pulled" through the 40S subunit during scanning.

ABSTRACTS OF ORAL PRESENTATIONS (FRIDAY)

SESSION IV: Clinical Research

Chair: Karen Kelly, MD

KEYNOTE LECTURE: AML: OFF THE BOULEVARD OF BROKEN DREAMS AND INTO THE FAST LANE

Brian Jonas, PhD, Associate Professor of Medicine, School of Medicine, University of California, Davis

Acute myeloid leukemia (AML) is a lethal bone marrow cancer caused by clonal expansion of immature and ineffective myeloid precursor cells. The five-year survival is estimated at around 25%. The disease is characterized clinically by bone marrow failure leading to infections, bleeding and anemia, and is rapidly fatal if untreated. AML is characterized by recurrent mutations and cytogenetic abnormalities, which, along with age, predict outcomes. The treatment paradigm for AML is undergoing rapid evolution driven by increased understanding of disease biology and development of targeted agents and rational therapies. Despite several attempts to get off the "Boulevard of Broken Dreams," the classic 7+3 regimen developed in the early 1970s remained the standard of care until 2017, when AML drug development jumped into the fast lane with nine new drugs approved by the FDA from 2017 to 2020. Our UC Davis Comprehensive Cancer Center AML research program has played a pivotal role in this new era in AML care through the testing of novel agents and combinations in clinical trials. For example, our contributions to the development of combination regimens of the BCL-2 inhibitor, venetoclax, with hypomethylating agents has helped change the practice of AML and led to FDA accelerated approval AML. We have also made major contributions to the development of an E-selectin inhibitor, uproleselan, and a FLT3 inhibitor, quizartinib, both of which have received FDA breakthrough designation for AML. We continue to focus on developmental therapeutics and testing of novel agents and combinations with the goal of continuing to improve outcomes for patients with AML.

UP IS DOWN AND DOWN IS UP—UPDATE ON DONOR SELECTION AND GvHD PREVENTION STRATEGIES IN ALLOGENEIC STEM CELL TRANSPLANTATION

Rasmus Hoeg, MD
Assistant Professor of Medicine
University of California, Davis

Donor selection in allogeneic transplantation depends on underlying malignancy, nature of remission, planned conditioning regimen and GvH prevention strategy. Particularly the latter aspect has changed dramatically in recent years, as the use of post-transplant cyclophosphamide has allowed the use of haplo-identical donors. Using post-transplant cyclophosphamide after haplo-identical transplantation has been shown to be a well-tolerated therapy with low risk of chronic GvHD. However, relapse risk after this strategy is high compared to standard transplant strategies. As post-transplant cyclophosphamide is now increasingly being used for matched sibling and unrelated donors, donor selection is becoming increasingly complex.

THE UCHMC MULTIPLE MYELOMA WORKING GROUP: SUCCESSES, SETBACKS, AND FUTURE DIRECTIONS

Aaron Seth Rosenberg, MD, MS
University of California, Davis

Multiple myeloma (MM) is a rare hematologic malignancy that accounts for between 1-2% of all malignancy diagnoses in the United States. Due to rarity, frequent presence of comorbidities and an increasingly robust treatment armamentarium, enrollment to MM trials can be challenging. In 2015, the University of California

Hematologic Malignancies Consortium was founded, and the MM working group was one of the first groups to open a trial at multiple UC sites. This initial study, UCHMC 1502, has now completed accrual and has taught us much about collaboration through the UCHMC structure. Our ongoing clinical research pipeline now includes trials throughout the relapsed space, and retrospective studies of high risk and populations of specific interest. This talk will provide a brief overview of the successes, and setbacks, in the UCHMC MM working group, along with some lessons learned and future directions.

THE FUTURE OF CELLULAR THERAPY

Mehrdad Abedi, MD
Professor of Medicine; Director, Alpha Stem Cell Clinic
University of California, Davis

Novel anti-cancer therapeutic agents has revolutionized the treatment of hematological malignancies and record number of targeted agents are being approved by FDA. Most of these treatments however do not cure the disease and continued therapy is needed. In most cases relapse of the disease even on treatment is inevitable. Cellular therapies in principle can have a curative potential with eradicating every single caner cells. They also can produce a memory response that can prevent future relapse of the disease, very similar to host immunity against infection. The current cellular therapy approaches such as CAR T cells, TCR based T cells and NK cells have shown promising results. The new gene engineering approaches are designing even more effective patient specific or off the shelf products that can be used for treating a wide variety of cancers.

POSTER PRESENTATIONS

Poster Index:

Poster Abstracts:

Thursday poster sessions:

Junior Investigators (Blocks A1 – A4): 12:10 – 12:45 PM
Junior Investigators (Block A5) and Faculty Investigators (Block B1): 12:50 – 1:25 PM

Friday poster sessions:

Junior Investigators (Blocks C1 – C4): 8:00 – 8:35 AM
Faculty Investigators (Blocks D1 – D2): 8:40 – 9:15 AM

POSTER PRESENTATION (INDEX)

THURSDAY POSTER SESSIONS – JUNIOR INVESTIGATORS

BLOCK A1 12:10–12:45PM (Three-minute presentation with four-minute Q&A each)

1. **Effect of a high-fat diet during late stages of pancreatic carcinogenesis in mice**
   Natalia E. Cortez, Aya S. Ead, Joanna Wirkus1, Brian V. Hong, Gerardo G. Mackenzie

2. **Second Primary Malignancy Risk among HIV-Uninfected and HIV-Infected Survivors of Hodgkin Lymphoma: a 30-Year Follow-Up Population-Based Study**
   Renata Abrahão, MD, PhD, MSc, Ann Brunson, Justine Kahn, Qian Li M, Aaron S Rosenberg, Ted Wun, Theresa HM Keegan

3. **A Qualitative Study of Oncologists' Perceptions of Barriers and Motivating Factors to Clinical Trial Enrollment among Adolescent and Young Adult Cancer Patients**
   Renata Abrahão MD, PhD, MSc, Elysia M. Alvarez, Hiba Naz, Crystal C. Romero, Austin Waters, Anne C. Kirchhoff, Melissa M. Gosdin, Brad H. Pollock, Theresa Keegan

4. **Association of Lymphoma Incidence and Lymphoma-Specific Survival with Pesticide Usage in California**
   Christina Poh, John McPherson, Joseph Tuscano, Qian Li, Arti Parikh-Patel, Christoph Vogel, Theresa Keegan

BLOCK A2 12:10–12:45PM (Three-minute presentation with four-minute Q&A each)

1. **Investigating the Role of the Aryl Hydrocarbon Receptor in ERBB4 Regulation**
   Daniel York, Danika Bannasch, Robert Rebhun

2. **MicroRNA-1291-5p sensitizes pancreatic carcinoma cells to arginine deprivation and chemotherapy through the regulation of arginolysis and glycolysis**
   Mei-Juan Tu, Zhijian Duan, Zhenzhen Liu, Chao Zhang, Richard J. Bold, Frank J. Gonzalez, Edward J. Kim, Ai-Ming Yu

3. **Repurposing amiloride derivatives in the targeting of cancer cells via lysosomal cell death**
   Michelle G. N. Hu, Anastasia L. Berg, Ashley R. Rowson-Hodel, Michael Keeling, Ruiwu Liu, Kit S. Lam, Kermit L. Carraway, III

4. **Distinct alterations of chromatin structure underlie cellular context-specific activities of RORγ inhibitors**
   Hongye Zou, Yatian Yang, Zhenrui Shi, Xuesong Wu, Hong-Wu Chen

BLOCK A3 12:10–12:45PM (Three-minute presentation with four-minute Q&A each)

1. **Novel role of glypican-3 in cancer-induced immunosuppression**
   Tsung-Chieh Shih, Yu-Jui Yvonne Wan

2. **A Pilot Study of Intratumoral SD-101 (Toll-like Receptor 9 Agonist), Nivolumab, and Radiotherapy for Treatment of Chemotherapy-refractory Metastatic Pancreatic Adenocarcinoma**
   Jasmine C. Huynh, MD, Justin A. Chen, Arta M. Monjazeb, May T. Cho, Edward J. Kim

3. **A Transformable Delivery System for the Effective Treatment of Pediatric Central Nervous System Tumors**
   Hao Wu, Hongwei Lu, Wenwu Xiao, Hongxu Du, Kit S Lam. Yuanpei Li, Tzu-Yin Lin

4. **Peripheral blood from relapsed and refractory neuroblastoma patients treated with internalized 131I-mIBG indicates time-dependent biomarkers of exposure out to 15 days**
   Angela C. Evans, David A. Edmondson, Katherine K. Matthay, M. Meaghan Granger, Araz Marachelian, Daphne A. Haas-Kogan, Steven G. DuBois, Matthew A. Coleman

5. **Mitochondria as a therapeutic target in the metabolic reprograming of glioblastoma (GBM)**
   Sandipan Datta, Thomas K. Sears, Kevin Woolard, James M. Angelastro, Gino A. Cortopassi

BLOCK A4 12:10–12:45PM (Three-minute presentation with four-minute Q&A each)

1. **Fluorescence Lifetime Imaging for Intraoperative Delenation of Oral and Oropharyngeal Cancers**
   Brent W Weyers, Mark Marsden, Takanori Fukazawa, Tianchen Sun, Julien Bec, Andrew C Birkeland, Regina F. Gandour-Edwards, Arnaud F Bewley,Marianne Abouyared, Athena K Tam, D Gregory Farwell, Laura Marcu

2. **Hybrid nanoplasmonic scaffold reveals the importance of the glycocalyx in liquid biopsy diagnostics using extracellular vesicles**
   Tatu Rojalin, Hanna J. Koster, Juanjuan Liu, Rachel R. Mizenko, Di Tran, Sebastian Wachsmann-Hogiu, Randy P. Carney

3. **Absorbed dose assessment in 90Y radioembolization patients: A comparaison between total-body PET EXPLORER and conventional PET imaging**
   G. Costa, B. Spencer, M. Rusnak, D. T. Caudle, C. Foster, C. T. Vu, E. Roncali

4. **The Expansion of the One-Bead-One-Compound Combinatorial Chemistry Toolbox**
   Lucas Solano, Kellie Weeks, Kit S. Lam

5. **Liver Segmentation in CT scans of Patients with Liver Cancer**
   Shaan S. Bhalaru, Amirtaha Taebi, Michael Rusnak, Denise T. Caudle, Catherine T. Vu, Emilie Roncali

BLOCK A5 12:50 - 1:25PM (Three-minute presentation with four-minute Q&A each)

1. **A CRISPR Screen to Expanding the Therapeutic Atlas for Cancer Treatment**
   J. Antonio Gomez, Colleen Sweeney, David J. Segal

2. **Incidence of Breakthrough Fungal Infections with Isavuconazole Versus Posaconazole Prophylaxis in AML Patients**
   Michael Wright, PharmD, Benjamin Moskoff

3. **Nuclear Receptor ROR-γ and kinase PBK Drive a Feed-forward Loop in Hyperactivating AR Signaling in mCRPC**
   Xiong Zhang, Zenghong Huang, Jin Li, Christopher P. Evans, Hong-Wu Chen

4. **Induction of BRCA2 Insufficiency, Genome Instability and Tumorigenesis by SYCP3**
   Ash Jay, Sumit Sandhu, Hang Phuong Le, Jie Liu, Alexander Borowsky, Neil Hunter, Wolf-Dietrich Heyer

THURSDAY POSTER SESSION – FACULTY INVESTIGATORS

BLOCK B1 12:50 - 1:25PM (Three-minute presentation with four-minute Q&A each)

1. **Engrailed-1 and epigenetic vulnerabilities in metastatic pancreatic cancer**
   Chang-il Hwang, Jae Seok Roe, Eunjung Lee, Jihao Reno Xu, Michael Hollingsworth, Christopher Vakoc, David Tuveson

2. **One-component new-chemical-entity nanomedicine (ONN) to target autophagy in cancers**
   Zhao Ma, Mythili Ramachandran, Dalin Zhang, Daniel P Vang, Gustavo Barisone, Joseph Tuscano, Yuanpei Li

FRIDAY POSTER SESSIONS – JUNIOR INVESTIGATORS

BLOCK C1 8:00–8:35AM (Three-minute presentation with four-minute Q&A each)

1. **Central Venous Catheter Placement in Neutropenic Pediatric Oncology Patients**
   S.C. Stokes, J.E. Jackson, C.M. Theodorou, K.J. Yamashiro, E.G. Brown

2. **Central Venous Catheter Placement in Pediatric Oncology Patients: What is the impact of thrombocytopenia?**
   S.C. Stokes, K.J. Yamashiro, C.M. Theodorou, J.E. Jackson, E.G. Brown

3. **Association Between a Protective Genetic Variant of Indigenous American Origin within the 6q25 Region and Subtype-Specific Breast Cancer Risk in Latin American Women**
   Valentina Zavala, Tatiana Vidaurre, Sandro Casavilca, Carlos Castañeda, Jeannie Vásquez, Fernando Valencia, Zaida Morante, Monica Calderon, Julio Abugattas, Henry Gómez, Hugo Fuentes, Ruddy Liendo Picoaga, Jose M. Cotrina, Zaida Morante, Fernando Valencia, C. Monge-Pimentel, Silvia Neciosup, Bizu Gelaye, Laura Fejerman

4. **Male breast cancer: characteristics and outcomes in California, 1988 to 2017**
   Frances B. Maguire, Brenda M. Hofer, Cyllene R. Morris, Arti Parikh-Patel, Candice A. Sauder, Theresa H. M. Keegan

5. **The Sacramento Area Breast Imaging Registry (SABIR): A Rich Resource for Breast Cancer Screening and Outcomes Research**
   Olivia Sattayapiwat, MS, MPH, Michael C.S. Bissell, Evan de Bie, Yang Vang, Diana L. Miglioretti

BLOCK C2 8:00–8:35AM (Three-minute presentation with four-minute Q&A each)

1. **Phase I/II Trial of BMS-986205 and Nivolumab as First Line Therapy in Hepatocellular Carcinoma**
   Jasmine Huynh, MD, Jingran Ji, Justin Chen, May Cho, Arta M Monjazeb, Sepideh Gholami, Kit Tam, Steven Colquhoun, Souvik Sarkar, Eric Chak, Christopher Bowlus, Catherine Vu, John McGahan, Michael Corwin, Ghaneh Fananapazir, Susan Stewart, Edward Kim

2. **Hepatocellular Carcinoma Treatment Using a Galectin 1 Inhibitor**
   Tsung-Chieh Shih, Ying Hu, Ruiwu Liu, Kit Lam, Yu-Jui Yvonne Wan

3. **Promoting 'Adaptive' NK Cell Response in Hematologic Cancers.**
   Joshua Meckler, Gustavo A. Barisone, Daniel Vang, William Murphy, Joseph Tuscano

4. **Nordihydroguaiaretic acid-based nanoparticles for potentiating the antitumor immunity induced by IDO inhibition**
   Xiangdong Xue, Ruonan Bo, Tzu-yin Lin, Arta M. Monjazeb, Yuanpei Li

5. **Analysis of tumor infiltrating NK and T cells highlights IL-15 stimulation and TIGIT blockade as a combination immunotherapy strategy for soft tissue sarcomas**
   Sean J. Judge, Morgan A. Darrow, Steve W. Thorpe, Alicia A Gingrich, Edmond F. O'Donnell, Alyssa R. Bellini, Ian R. Sturgill, Logan V. Vick, Cordelia Dunai, Kevin M. Stoffel, Yue Lyu, Shuai Chen, May Cho, Robert B. Rebhun, Arta M. Monjazeb, William J. Murphy, Robert J. Canter

BLOCK C3 8:00–8:35AM (Three-minute presentation with four-minute Q&A each)

5. **MiR-124-3p signaling in the control of cancer cell adhesion complexes and invadopodia**
   Ling-Long Deng, Hannah Petrek, Mei-Juan Tu, Ai-Ming Yu

6. **Distinguishing Tumor Margins in Glioblastoma multiforme using FLIm**
   Silvia Noble Anbunesan, Alba Alfonso-Garcia, Julien Bec, Matthew Bobinski, Mirna Lechpammer, Oluwaseun Adeola Omofoye, Orin Bloch, Laura Marcu

7. **Designer Edible Crops to deliver anti-cancer compounds**
   Collin R. Barnum, Morgan P. Connolly, Justin B. Siegel, Patrick M. Shih

8. **Ultralow-Dose CT Imaging with Deep Learning Noise Reduction on the EXPLORER Total-Body PET/CT Scanner**
   Jesse Ahlquist, Yasser G. Abdelhafez, Lorenzo Nardo, Ramsey D. Badawi, Jinyi Qi, Guobao Wang

BLOCK C4 8:00–8:35AM (Three-minute presentation with four-minute Q&A each)

1. **Therapeutic targeting of ROR-γ induces genome-wide reprogramming of chromatin landscapes in prostate cancer**
   Yatian Yang, Junjian Wang, Hongye Zou, Christopher P. Evans, Hong-Wu Chen

2. **Microbial Metabolite Mimicry, a Nano-drug for Colon Cancer Treatment**
   Ying Hu, Ruiwu Liu, Kit S. Lam, Yu-Jui Yvonne Wan

3. **Bladder cancer metabolomics identifies important differences in lipid metabolites between metastatic and non-metastatic tumors**
   M. Malvina Tsamouri, DVM, Shamira Sridharan, Blythe P. Durbin-Johnson, Marc A. Dall'Era, Paramita M. Ghosh

4. **Mismatch repair proteins regulate homologous recombination to prevent genome rearrangements**
   Diedre Reitz, John McPherson, Wolf-Dietrich Heyer

5. **Bioengineered microRNAs in the control of folate cycle related one-carbon metabolism in NSCLC metabolism**
   Yixin Chen, Zhenzhen Liu, Mei-Juan Tu, Neelu Batra, Ai-Ming Yu

FRIDAY POSTER SESSIONS – FACULTY INVESTIGATORS

BLOCK D1 8:40 – 9:15AM (Three-minute presentation with four-minute Q&A each)

1. **Total-Body Dynamic PET of Metastatic Cancer: First Patient Results**
   a. Guobao Wang, PhD, Mamta Parikh, Lorenzo Nardo, Yang Zuo, Yasser G. Abdelhafez, Jinyi Qi, Terry Jones, Patricia M. Price, Simon R. Cherry, Chong-Xian Pan, Ramsey D. Badawi

2. **Cross-resistance among next generation anti-androgen drugs through the AKR1C3/AR-V7 axis in advanced prostate cancer**
   a. Jinge Zhao, Shu Ning, Wei Lou, Joy C. Yang, Christopher P. Evans, Allen C. Gao, Chengfei Liu

3. **The role of AXL tyrosine kinase in the tumor-immune microenvironment of melanoma**
   a. Walsh, A. Gingrich, A. Meerlov, R. Nielsen, R. Canter, E.M. Maverakis, A.R. Kirane

4. **Biomarker Analysis of Neoadjuvant Intralesional Therapy in High Risk Melanoma**
   a. S. Gholami, S. Chen, R. Nielsen, R. Bold, R. Canter, E.M. Maverakis, A.R. Kirane

BLOCK D2 8:40 – 9:15AM (Three-minute presentation with four-minute Q&A each)

1. **Bi- and tri-specific antibodies for hematologic malignancies and solid tumors.**
   Gustavo A. Barisone, Daniel Vang, Joshua Meckler, William Murphy, Joseph Tuscano

2. **Pro-tumorigenic effects of olfactomedin-like 3 in glioma**
   R.G. Toedebusch, L.A. Wittenburg, L.M. Joseph, E.T. Debebe, C.M. Toedebusch

3. **Impact of the Aryl Hydrocarbon Receptor signaling pathway in Breast Cancer development**
   Christoph F. A. Vogel, Gwendal Lazennec, Francis He, Alejandro Castaneda, Yasuhiro Ishihara, Sarah Y. Kado, Carla Dahlem, Thomas Haarmann-Stemmann, Colleen Sweeney

THURSDAY POSTER PRESENTATIONS (ABSTRACTS)

BLOCK A1 12:10–12:45PM

1. EFFECT OF A HIGH-FAT DIET DURING LATE STAGES OF PANCREATIC CARCINOGENESIS IN MICE

Natalia E. Cortez, Aya S. Ead, Joanna Wirkus, Brian V. Hong, Gerardo G. Mackenzie
Department of Nutrition, University of California, Davis, CA

Background: Pancreatic cancer is one of the top cancer-associated deaths in the United States, with a 5-year mortality rate of ~90%. Obesity is an established risk factor for pancreatic cancer. Previous studies have shown that a high-fat diet (HFD) accelerates pancreatic cancer progression by increasing systemic inflammation, and that male mice develop more aggressive tumors earlier than female mice. Several pathways have been implicated in the rapid progression of pancreatic cancer, such as the PI3K/Akt pathway, CCK receptor pathway, and Wnt/beta-catenin pathway. However, the mechanisms by which dietary fat affects pancreatic cancer progression at later stages of development remains unclear.

Objective: To determine if a high-fat diet influences late stages of pancreatic cancer progression in a clinically relevant, genetically-engineered LSL-KrasG12D/+; pft1aCre/+ (KC) model of pancreatic cancer.

Methods: KC mice were fed a chow-diet until 6 months of age. At that time, male and female KC mice (6-9 per group per sex) were randomized and fed, either, a control diet (CD; 20% calories from fat) or a high-fat diet (HFD; 40% calories from fat) for 3 or 6 months. Forelimb grip strength, body composition, blood glucose, and ketone levels were assessed. After 3 or 6 months of dietary intervention, mice were euthanized and tissues were harvested for further analysis.

Results: After 6 months of HFD intake, body weight increased 13% and 14% in female and male KC mice, respectively, compared to CD-fed mice, although this increase was not significantly different. KC mice fed a HFD for 3 months showed no increase in pancreas/tumor weight when compared to those fed a CD. However, a 43% increase in pancreas/tumor weight was observed in female KC mice fed a HFD for 6 months. In contrast, no difference in pancreas/tumor weight was observed in male mice between the two dietary groups. In addition, no significant differences were observed in liver, lungs, spleen, heart, or gastrocnemius weights between the dietary groups. Moreover, the grip strength performance was comparable between the CD-fed mice and the HFD-fed mice.

Conclusions: Our preliminary findings indicate that a high-fat diet fed at a later stage in the pancreatic cancer development selectively increases pancreatic tumor weight in female mice, but not in male mice. Further analysis are in progress to evaluate the mechanisms on how obesity contributes to pancreatic carcinogenesis and the effects of high-fat and low-fat diets on pancreatic cancer progression.

Funding: Supported by funds from the University of California, Davis to GGM. NEC is supported with a fellowship from UC-MEXUS

2. SECOND PRIMARY MALIGNANCY RISK AMONG HIV-UNINFECTED AND HIV-INFECTED SURVIVORS OF HODGKIN LYMPHOMA: A 30-YEAR FOLLOW-UP POPULATION-BASED STUDY

Renata Abrahão MD, PhD, MSc[1,2], Ann Brunson, MS[1], Justine Kahn, MD, MS[3], Qian Li M.[1], Aaron S. Rosenberg[1], Ted Wun[1], Theresa H.M. Keegan[1]
[1]Center for Oncology Hematology Outcomes Research and Training (COHORT), Division of Hematology and Oncology, University of California, Davis, School of Medicine, Sacramento-CA; [2]Center for Healthcare Policy and Research, University of California, Davis, School of Medicine, Sacramento-CA; [3]Department of Pediatrics, Division of Hematology, Oncology and Stem Cell Transplantation, Columbia University, New York, NY.

Introduction: Second primary malignancy (SPM) is one of the most devastating late complications following Hodgkin lymphoma (HL) treatment. Historically, the most common SPMs in patients treated for HL are solid tumors, which are largely related to radiation exposure during initial therapy. For the last three decades, efforts to address the risk of SPM after HL therapy have focused on reducing exposure to radiation, as well as refining the approach for patients where radiation is indicated. To date, few population-based studies in the United States have quantified the burden of SPMs and evaluated the potential effect of changes in therapeutic management over time. Additionally, to our knowledge, no study has compared SPM risk between human immunodeficiency virus (HIV)-infected and HIV-uninfected HL survivors.

Methods: We used data from the California Cancer Registry on 21,043 patients diagnosed with primary HL between 1988 and 2015 with follow-up through 2017. We calculated standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs) and absolute excess risks (AERs) to compare SPM incidence in our HL cohort with the expected number of first primary cancer incidence in the general California population, based on patient's age at diagnosis (5-year categories), sex, calendar year (3-year intervals), cancer site, and race/ethnicity. SIRs are presented by HIV status, SPM latency, treatment era, and cancer type. P-values for trends were used to examine whether SPM risk changed over time.

Findings: Among 20,303 HIV-uninfected patients (median follow-up of 14.1 years), overall SPM risk was increased 1.95-fold compared with the general population (SIR=1.95, 95% CI 1.86–2.04). In 740 HIVinfected patients (median follow-up of 11.7 years), overall risk was increased 2.68-fold compared with the general population (SIR=2.68, 95% CI 2.0–3.40), translating to an 37% higher incidence of SPM in HIVinfected vs. HIV-uninfected patients. The AER (per 10,000 person-years) of SPM was 43.1 in HIV-uninfected and 76.5 in HIV-infected patients, resulting in a 33.4 excess SPM per 10,000 person-years in HL survivors with HIV. Malignancies that contributed the most to overall AER were non-Hodgkin lymphoma (NHL), female breast and lung cancers in HIV-uninfected patients; and Kaposi sarcoma, NHL, anorectal and head & neck (HNC) cancers in HIV-infected patients. Notably, among HIV-uninfected patients, the highest overall risk of SPM occurred ≥20 years after diagnosis (SIR= 2.27, 95% CI 1.99–2.58) (Figure). In contrast, the highest overall risk in HIV-infected patients was observed <2 years after diagnosis (SIR=4.42, 95% CI 2.53–7.19). Radiation used decreased from 46.9% in 1988–1996 to 29.5% in 2007–2015. Among HIV-uninfected patients, there was a trend towards decreased risk over time of overall and selected solid SPMs (lung, female breast, and gastrointestinal cancers) (Table). In an analysis restricted to HIV-uninfected patients who received radiation irrespective of chemotherapy, findings also suggested a declined risk of overall and selected solid SPMs over time: any solid (SIR=2.15 in 1988–1996 and SIR=1.30 in 2007–2015, p<0.0001), lung (SIR=3.69 in 1988–1996 and SIR=1.81 in 2007–2015, p=0.0031), and female breast (SIR=2.95 in 1988–1996 and SIR=0.63 in 2007–2015, p<0.0001).

Conclusion: Compared with the general population, the risk of developing a SPM following HL treatment was significantly higher among both HIV-uninfected and HIV-infected patients, with the absolute excess risk greater for those with HIV infection. There were different temporal patterns and types of SPM between HIVuninfected and HIV-infected patients. These findings prompt the question on whether earlier and/or more intensive cancer screening should be pursued for HIV-infected survivors. The trend towards decreased risk for selected solid SPMs among HIV-uninfected patients, especially lung and female breast cancers, suggest that strategies to reduce radiation in HL survivors may be working. Despite promising trends in this group, the observation that SPM risk was highest ≥20 years after initial therapy further highlights the need for long-term surveillance and survivorship care in this at-risk population.

3. A QUALITATIVE STUDY OF ONCOLOGISTS' PERCEPTIONS OF BARRIERS AND MOTIVATING FACTORS TO CLINICAL TRIAL ENROLLMENT AMONG ADOLESCENT AND YOUNG ADULT CANCER PATIENTS

Renata Abrahão, MD, PhD, MSc [1,2] Elysia M. Alvarez[1,3], Hiba Naz,[2] Crystal C. Romero[3], Austin Waters[4], Anne C. Kirchhoff[4,5], Melissa M. Gosdin[2], Brad H. Pollock[6], Theresa H.M. Keegan[1]
[1]Center for Oncology Hematology Outcomes Research and Training (COHORT), Division of Hematology and Oncology, University of California Comprehensive Cancer Center, Sacramento-CA; [2]Center for Healthcare Policy and Research, University of California Davis, Sacramento-CA; [3]Department of Pediatrics, UC Davis Health System, Sacramento-CA, [4]Cancer Control and Population Sciences, Huntsman Cancer Institute, Salt Lake City, Utah; [5]Department of Pediatrics, University of Utah, Salt Lake City, Utah, [6]Department of Public Health Sciences, University of California Davis, Sacramento-CA

Introduction: Over the past 30 years, cancer survival among adolescents and young adults (AYAs, 15 to 39 years) has not improved to the same extent as in pediatric and older adult cancer patients. One of the factors that may contribute to poor outcomes in this population is low clinical trial participation. Even when provided access to a trial, AYAs are less likely to participate than children, highlighting the importance of understanding physician and patient factors that influence trial enrollment. To date, there is limited research on physician and AYA patient attitudes, motivations and barriers toward clinical trial enrollment. Here we report on preliminary results from oncologist interviews regarding enrollment of AYA cancer patients onto clinical trials.

Methods: From December 2019 to August 2020 we conducted 17 semi-structured interviews with oncologists who treat AYA cancer patients, 8 in California and 9 in Utah. Participants were recruited at UC Davis Comprehensive Cancer Center (UCDCCC), Rideout Cancer Center, and Tahoe Cancer Center in Northern California, as well as at Huntsman Cancer Institute and Primary Children's Hospital in Utah. Interviews were conducted in-person or over the phone by one interviewer in each state. Two of the study authors from UCDCCC independently analyzed interview transcripts and iteratively developed a codebook until consensus was reached (after 4 interviews were coded). The 2 researchers further coded the remaining transcripts and created a framework matrix to summarize and analyze the data.

Findings: Of the 17 physicians interviewed, 7 were pediatric and 10 were medical hematologist/oncologists. We identified several themes regarding barriers to and motivation and facilitators for trial enrollment, as well as potential strategies for improvement. Participants described four main physician barriers to enrolling AYA patients in cancer clinical trials, including: 1) lack of open trials for AYAs, especially for those with rare diseases; 2) strict eligibility criteria, particularly for pharmaceutical company trials; 3) lack of awareness of some primary care physicians about the urgency of the disease and/or the availability of open cancer trials, leading to a delayed referral to a specialized cancer center; and 4) lack of communication between pediatric and medical hematologists/oncologists regarding open trials that could be beneficial for AYA patients. The main motivating factors oncologists have for enrolling AYA patients on clinical trials are the provision of best care for the patient and the gain in scientific knowledge that can guide treatment improvements. Barriers oncologists noted for AYA patients included: 1) hospital distance; 2) clinical trials requiring additional procedures and visits to the hospital, increasing the potential financial burden; 3) lack of psychosocial support; 4) lack of patient understanding of the trial benefits; 5) AYA psychological barriers; 6) fertility concerns and, to a lesser extent, 7) distrust in research. Physicians identified major AYAs motivators as: 1) access to potentially better treatment compared to standard treatment, 2) the altruistic attitude of helping other AYA cancer patients and contributing to science, 3) financial incentives (e.g. gas cards, free meals and housing), and 4) access to new drugs and tests, especially when the disease is severe or relapses and there are no other options outside the trial. Potential ways to improve AYA trial enrollment include: 1) increasing availability of trials for AYAs with more inclusive eligibility criteria; 2) improving dissemination of information about open trials inside and outside the physicians' institutions (e.g., weekly emails and AYA tumor boards within each cancer sub-specialty); 3) "bridging the gap" between pediatric and adult oncologists, so AYAs do not miss the opportunity for enrollment; 4) providing financial and psychosocial support (e.g., through social workers); 6) increasing the time a physician has available to explain the trial and enroll the patient; 7) providing multimedia communications strategies to supplement trial education (e.g. a short video explaining the trial or a semi-interactive tool that could help to explain the informed consent; 8) providing access to peer support; 9) having patient navigators,

especially for patients with limited resources; and 10) offering physician education on ways to better communicate the trial to AYA cancer patients.

Conclusion: AYA cancer patients are a unique population with historically lower participation in clinical trials. We identified major barriers and motiviating factors to AYA enrollment in clinical trials from the perspective of the physicians and suggested potential areas for improvement. As a next step, we will complete the analysis of 26 AYA patients interviews in order to identify barriers, motivations and facilitators to trial participation from their perspectives and explore additional potential areas for improvement.

4. ASSOCIATION OF LYMPHOMA INCIDENCE AND LYMPHOMA-SPECIFIC SURVIVAL WITH PESTICIDE SSAGE IN CALIFORNIA

Christina Poh[1,2], John McPherson[1,3], Joseph Tuscano[1,4], Qian Li[1], Arti Parikh-Patel[5], Christoph Vogel[6], Theresa Keegan[1]

[1]Division of Hematology/Oncology, UC Davis Comprehensive Cancer Center; [2]Division of Medical Oncology, University of Washington; [3]Department of Biochemistry and Molecular Medicine, UC Davis; [4]Veterans Administration, Northern California Healthcare System; [5]California Cancer Reporting and Epidemiologic Surveillance Program, UC Davis; [6]Department of Environmental Toxicology and the Center for Health and the Environment, UC Davis

Introduction: While previous studies propose pesticide exposure to be a risk factor for non-Hodgkin lymphoma (NHL) development, little is known about the prognosis and molecular basis of pesticide-related NHL. Genotoxicity and reactive oxygen species generation in healthy cells by pesticides used for agricultural production is likely involved in the transformation of healthy lymphocytes into clonal ones. Prolonged environmental exposure could lead to clonal expansion of cells with specific tumorigenic alterations and immunodeficiency, potentially contributing to pathogenesis and resistance. Chronic exposure could also lead to adaptive mechanisms for DNA repair and antioxidant activity, undermining chemotherapy regimens. A recent retrospective study found pesticide occupational exposure to be associated with treatment failure and poorer survival, highlighting the need for studies examining the biology of these tumors. Studies to date have focused on the epidemiology of pesticide exposure, with little or no tumor analysis to identify pesticide related mutational signatures that could impact treatment and prognosis.

Methods: Using the California Cancer Registry, we identified patients with a first primary diagnosis of NHL from 2010-2016 and linked these patients with CalEnviroScreen 3.0 to obtain production agriculture pesticide exposure to 70 chemicals from the state mandated Pesticide Use Reporting (PUR) by census tract from 2012-2014. In addition, data from the PUR were integrated into a geographic information system tool that also uses land use data to estimate cumulative exposure to specific pesticides previously associated with NHL (glyphosate, organophosphorus, carbamate, phenoxyherbicide and 2,4-dimethylamine salt) between 10 years prior up to 1 year after NHL diagnosis. We used SEER*Stat software to calculate NHL subtype incidence rates by census tract pesticide use level. Multivariable cox proportional hazards regression models were used to evaluate the impact of pesticide exposure on lymphoma-specific survival. Further, we performed in vitro studies investigating EBV-transformed B lymphoblastoid cell lines for expression of genes related to NHL and carcinogenesis upon exposure to 4 different pesticides (glyphosate, dichlorodiphenyltrichloro ethane (DTT), hexachlorobenzene (HCB) and chlorpyrifos).

Results: Among 40,879 NHL patients identified, 37.1% were exposed to pesticide in their census tract of residence, with 10.9% in low, 13.0% in mid and 13.1% in high pesticide exposure census tracts. Glyphosate, organophosphorus, carbamate, phenoxyherbicide and 2,4-dimethylamine salt exposure was reported in 34.1%, 26.0%, 10.6%, 14.0% and 12.8% of NHL patients, respectively. Pesticide exposure was not associated with increased NHL incidence by NHL subtype or subgroups defined by sociodemographic factors. In addition, we found no association between pesticide exposure or varying pesticide exposure levels and lymphoma-specific survival in any of the NHL subtypes considered. The expression analysis of biomarkers relevant in NHL and carcinogenesis showed that treatment with chlorpyrifos, glyphosate, and DDT led to elevated levels of IL-22 mRNA in EBV-transformed Co88BV lymphoma cells. No significant effect by HCB was found. IL-22 produces proliferative and anti-apoptotic signaling and has been identified as a cancer-promoting cytokine.

Conclusion: Pesticide exposure is commonly reported among patients with NHL. Our population analysis found no association between pesticide exposure and NHL incidence or lymphoma-specific survival. Further correlative and molecular studies including DNA damage signature analysis and RNA sequencing to identify biomarkers which associate with pesticide exposure are ongoing.

BLOCK A2 12:10–12:45PM

1. INVESTIGATING THE ROLE OF THE ARYL HYDROCARBON RECEPTOR IN ERBB4 REGULATION

Daniel York[1], *Danika Bannasch*[2], *Robert Rebhun*[1]
[1]*University of California at Davis, School of Veterinary Medicine, Department of Surgical and Radiological Sciences.* [2]*University of California at Davis, School of Veterinary Medicine, Department of Population Health and Reproduction*

Cancer is the leading cause of death in Golden Retrievers. Recent estimates of cancer-associated mortality in the breed are in excess of sixty-percent, with reported median lifespans ranging from 9-12 years of age. Combining genome wide association (GWAS), whole genome sequencing and fragment analysis data, we identified an indel located within the ERBB4 5'UTR that was significantly associated with longer lifespan and decreased cancer in Golden Retrievers. Transcription factor binding analyses revealed that the indel (6-base pair deletion) represented a core motif of the dioxin response element (DRE), which is the binding site for the transcription factor aryl hydrocarbon receptor (AHR). Preliminary gene expression data showed that canine ERBB4 is down regulated in canine cell lines treated with the AHR agonist indol-3-carbinol (I3C) and data from Chromatin Immunoprecipitation (ChIP) assays revealed that AHR binds to the ERBB4 5'UTR with up to 14-fold enrichment relative to control. These preliminary data lead us to hypothesize that ERBB4 is regulated by AHR and that regulation is altered by the indel identified in the 5'UTR. To confirm this regulatory mechanism, canine cells were treated with a combination of AHR agonists and siRNA and ERBB4 gene expression was monitored. Expression of CYP1A1, which is highly regulated by AHR, was used as a control. As expected, AHR agonists I3C and FICZ increased expression of CYP1A1 while treatment with the AHR siRNA resulted in decreased expression of CYP1A1 and AHR. When used together, pre-treating the cells with an AHR siRNA prior to I3C exposure prevented the I3C-induced CYP1A1 expression. This same affect, however, was not observed with ERBB4. Although ERBB4 is down regulated in canine cell lines treated with I3C, pre-treatment with AHR siRNA had no affect on the I3C-induced decrease in ERBB4. In addition, no affect on ERBB4 expression was observed following treatment with AHR siRNA alone, the AHR agonist FICZ, or the AHR antagonist SR1.This was observed in several canine cell lines and was independent of the 5'UTR indel, suggesting that the I3C-induced down regulation of ERBB4 is not AHR dependent. Additional studies using comprehensive ChIPseq and RNAseq analysis are underway to elucidate the AHR regulatory pathway in dogs and potentially uncover secondary or indirect mechanisms involved in ERBB4 regulation as well as evaluate the impact of the ERBB4 5'UTR indel on RNA stability.

Acknowledgements: Funding for this project was provided by the UC Davis Cancer Center and the Center for Companion Animal Health.

2. MICRORNA-1291-5P SENSITIZES PANCREATIC CARCINOMA CELLS TO ARGININE DEPRIVATION AND CHEMOTHERAPY THROUGH THE REGULATION OF ARGINOLYSIS AND GLYCOLYSIS

Mei-Juan Tu[1], Zhijian Duan[1], Zhenzhen Liu[1], Chao Zhang[1], Richard J. Bold[2], Frank J. Gonzalez[3], Edward J. Kim[2], Ai-Ming Yu[1]
[1]Department of Biochemistry & Molecular Medicine, UC Davis School of Medicine, Sacramento, CA [2]Division of Hematology and Oncology, Department of Internal Medicine, UC Davis School of Medicine, Sacramento, CA [3]Laboratory of Metabolism, National Cancer Institute, National Institutes of Health, Bethesda, MD

Cancer cells are dysregulated and addicted to continuous supply and metabolism of nutritional glucose and amino acids (e.g., arginine) to drive the synthesis of critical macromolecules for uncontrolled growth. Recent studies have revealed that genome-derived microRNA-1291-5p (miR-1291-5p or miR-1291) may modulate the expression of argininosuccinate synthase (ASS1) and glucose transporter protein type 1 (GLUT1). We also developed a novel approach to produce recombinant miR-1291 agents for research, which are distinguished from conventional chemo-engineered miRNA mimics. Herein, we firstly demonstrated that bioengineered miR-1291 agent was selectively processed to high levels of target miR-1291-5p in human pancreatic cancer (PC) cells. Following the suppression of ASS1 protein levels, miR-1291 perturbed arginine homeostasis and preferably sensitized ASS1-abundant L3.3 cells to arginine deprivation therapy. In addition, miR-1291 treatment reduced the protein levels of GLUT1 in both AsPC-1 and PANC-1 cells, leading to a lower glucose uptake (deceased > 40%) and glycolysis capacity (reduced approximately 50%). As a result, miR-1291 significantly improved cisplatin efficacy in the inhibition of PC cell viability. Our results demonstrated that miR-1291 was effective to sensitize PC cells to arginine deprivation treatment and chemotherapy through targeting ASS1- and GLUT1-mediated arginolysis and glycolysis, respectively, which may provide insights into understanding miRNA signaling underlying cancer cell metabolism and development of new strategies for the treatment of lethal PC.

3. REPURPOSING AMILORIDE DERIVATIVES IN THE TARGETING OF CANCER CELLS VIA LYSOSOMAL CELL DEATH

Michelle G. N. Hu, Anastasia L. Berg, Ashley R. Rowson-Hodel, Michael Keeling, 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

Our previous studies indicate that hydrophobic derivatives of the potassium-sparing diuretic amiloride specifically kill breast cancer cells independent of molecular profile, proliferative status, or species of tumor cell origin. Importantly, derivatives such as hexamethylene amiloride (HMA) are poorly cytotoxic toward non-transformed cells derived from a variety of tissues, pointing to a therapeutic window that might be exploited in the development of novel anti-cancer agents. Moreover, cytotoxicity occurs via a caspase (apoptosis)-independent mechanism triggered upon lysosomal membrane permeabilization (LMP), or breach of the limiting membrane of the lysosome, raising the possibility that such agents could efficiently target tumor cell populations that are resistant to apoptosis-inducing therapeutics. Here we demonstrate that a newly designed and synthesized amiloride derivative called LLC1 exhibits similar effects on tumor cells as HMA, but with even greater potency. We first demonstrate that HMA and LLC1 are cytotoxic toward cultured cells derived from a variety of tumor types, pointing to the potential wide application of this strategy toward many cancers. Moreover, we demonstrate that HMA and LLC1 induce LMP and necrotic cell death, reflected in the rupture of the plasma membrane. Finally, we observe the amiloride derivatives induce reactive oxygen species (ROS) production within breast cancer cells, and that drug-induced LMP is dependent upon ROS. Given that LMP is the hallmark of lysosome-dependent cell death, our observations suggest that amiloride derivatives might be repurposed to attack tumor cell subtypes resistant to apoptosis-inducing agents by engaging necrotic signaling via ROS.

4. DISTINCT ALTERATIONS OF CHROMATIN STRUCTURE UNDERLIE CELLULAR CONTEXT-SPECIFIC ACTIVITIES OF RORΓ INHIBITORS

Hongye Zou[1], *Yatian Yang*[1], *Zhenrui Shi*[2], *Xuesong Wu*[2], *Hong-Wu Chen*[1]
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We previously identified nuclear receptor ROR-γ as a novel therapeutic target in advanced prostate cancer (PCa) and triple-negative breast cancer (TNBC). Studies also showed that its T cell-specific form ROR-γt is essential for differentiation of T helper 17 (Th17) cells and that ROR-γt is an attractive target for IL-17-associated autoimmune diseases. We and others have identified several structurally distinct, small-molecule inhibitors/antagonists of the receptor. However, there has not been any direct comparison between the different ROR-γ inhibitors regarding their cellular activities and underlying mechanism of action (MOA). Here, we found that a panel of six chemically distinct inhibitors displayed very different activities in suppression of RORγ-mediated induction of gene expression. Specifically, when compared with the other three compounds, XY018 and GSK805 showed a modest activity in inhibiting interleukin 17 (IL-17) production in Th17 cells. In contrast, XY018 and GSK805 were highly potent in inhibition of cholesterol biosynthesis gene program in triple negative breast cancer (TNBC) cells and proliferation of the TNBC cells. Our further examinations showed that compounds that were potent in inhibition of IL-17 in normal mouse Th17 cells were largely inactive in suppression of IL-17 in mouse lymphoma cells whereas compounds that were inactive in Th17 became potent in the lymphoma cells. Our mechanistic study using ATAC-seq revealed that potency in altering chromatin accessibility at the loci of ROR-γ target genes constitutes a major mechanism underlying the distinctions in disruption of ROR-γ control of gene expression. Together, our study provides for the first-time evidence of tissue-selective modulator activities of the ROR-γ inhibitors and highlights compound action at chromatin level as a primary indicator of their tissue-selective potency in further development of ROR-γ tissue-selective modulators.

Funding: This work was supported in part by the Prostate Cancer Foundation (PCF) Challenge Award, a grant from NIH (R01CA224900), and by the UC Davis Comprehensive Cancer Center.

BLOCK A3 12:10–12:45PM

1. NOVEL ROLE OF GLYPICAN-3 IN CANCER-INDUCED IMMUNOSUPPRESSION

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Hepatocellular carcinoma (HCC) has poor prognosis (5-year survival of 15%) and is a leading cause of increased death for liver cancer patients. The major risk factors of HCC include cirrhosis, hepatitis B- and hepatitis C-virus infection, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), obesity, and diabetes. Sorafenib is the only FDA-approved therapy for patients with advanced HCC, with median survival limited to <11 months. HCC is typically an inflammation-associated cancer that can be immunogenic. Based on a 154-patient cohort of CheckMate-040 (NCT 01658878), checkpoint blockade nivolumab (clinical anti-PD-1 mAb) was approved by FDA on September 23, 2017, for the treatment of patients with HCC in those did not respond to sorafenib. However, only 14% of patients (22/154) had positive response to nivolumab. In the cancer patients, cancer cells triggered production of multiple immunosuppressive factors such as TGF-β and IL-10 and lead to immunosuppressive cascades including suppression of dendritic cells (DCs) maturation and the generation of possible DCregs showing low IL-12 production, high ILT-3 and ILT-4 expression and less T cell stimulatory activities. However, how cancer cells induce the immunosuppressive cascades remains unclear. Glypican-3 (GPC3), a member of the glypican family that attaches to the cell surface by a glycosylphosphatidylinositol (GPI) anchor, is overexpressed in 72%-81% of HCC cases and is elevated in the serum of a large proportion of patients with HCC. GPC3 was found to stimulate HCC growth through the activation of Wnt/β-catenin signaling pathway, which is the most frequently activated pathway in

liver carcinogenesis. We further investigate how GPC3/Wnt/β-catenin modulates the immune microenvironment of the tumor. Our data showed that condition medium (CM) from GPC3-expressing HCC cells can impair DCs maturation, and such immunosuppressive activity was reduced by knocking down GPC3 in HCC cells. Production of IFN-γ from the T cells was decreased by impaired DCs treated with CM from GPC3-expressing HCC cell lines. These phenotypic changes were restored by GPC3 knockdown in HCC cells. These results indicated that activated GPC3/Wnt/β-catenin signaling may account for the impaired function of immune cells and thereby limiting the efficacy of checkpoint immunotherapy in HCC.

Acknowledgements: The study was in part supported by The Cancer and Microbiome (CaM) Initiative Pilot Grant.

2. A PILOT STUDY OF INTRATUMORAL SD-101 (TOLL-LIKE RECEPTOR 9 AGONIST), NIVOLUMAB, AND RADIOTHERAPY FOR TREATMENT OF CHEMOTHERAPY-REFRACTORY METASTATIC PANCREATIC ADENOCARCINOMA

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Background: Pancreatic adenocarcinoma is an aggressive disease projected to be the second leading cause of cancer-related death. A majority of patients have advanced disease on diagnosis. Combination chemotherapy is first-line for advanced disease but limited by toxicity and median survival under 1 year. SD-101 is a toll-like receptor 9 agonist that is injected intratumorally to increase immunogenicity in the tumor microenvironment. Localized radiation can further enhance this via antigen release and potential abscopal effects. Immunotherapy has revolutionized care for various solid organ malignancies but not yet for pancreatic cancer. Therefore, the combination of SD-101, localized radiation, and checkpoint inhibitor is a promising therapeutic strategy for metastatic pancreatic adenocarcinoma.

Methods: Six patients with chemotherapy-refractory, liver-metastatic pancreatic adenocarcinoma will be evaluated for combination SD-101, radiation, and nivolumab. SD-101 is injected intratumorally into a liver metastasis on days 1, 8, 15, 29 with optional dosing days 43 and 57. Localized radiation (6-10 Gy) to the injected lesion will be given on days 1, 3, 5, 8, and 10. Nivolumab will be given at 240 mg every 2 weeks starting day 2 until progression or unacceptable toxicity. Blood samples will be collected at baseline and at regular intervals while on treatment. Biopsies will be obtained at baseline and on day 29.

Primary objectives are to evaluate safety and tolerability, defined as: if ≥5 patients reach day 29 without experiencing grade ≥3 treatment-related toxicity. Secondary objectives include preliminary efficacy as defined by disease control rate, duration of response, progression-free survival, and overall survival. Exploratory objectives include objective response rate and biomarker correlatives (T-cell clonality, tumor mutational burden, tumor infiltrative immune cell subsets, and immune-related gene expression profile). Blood and biopsy specimens will be analyzed using flow cytometry, qRT-PCR, RNA sequencing, and whole exome sequencing including immunohistochemistry on biopsy specimens.

3. A TRANSFORMABLE DELIVERY SYSTEM FOR THE EFFECTIVE TREATMENT OF PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

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Malignancies of the central nervous system (CNS) are the most common type of solid tumor affecting children and a leading cause of cancer-related death in children. With the deterioration of brain tumors, blood-brain barrier (BBB)/blood-brain tumor barrier (BBTB) with poor permeability, and relatively weak enhanced permeability and retention effect become major obstacles in delivering therapeutics to brain tumors. Vincristine (VCR) is a mainstay of treatment of a variety of cancers including brain tumors due to its well-defined

mechanism of action and demonstrated anticancer activity. However, the clinical application of VCR in brain tumors was limited by its neurotoxicity and inability to penetrate BBB/BBTB resulting in unsatisfactory anti-cancer efficacy. In this project, we developed a transformable sequential targeting in Crosslink (STICK) nanoparticle, which is capable of overcoming several important barriers for drug delivery to CNS tumors resulting in better efficacy and toxicity profile. STICK-NP was stable during circulation due to crosslinking and could transpass BBB/BBTB through glucose receptor (GLUT1)-mediated transcytosis. STICK-NP could further transform into smaller nanoparticle upon encountering acidic microenvironment and revealed hidden moiety to target tumor surface overexpressed sialic acid. STICK-NP employed a unique strategy which could sequentially target BBB/BBTB and brain tumor cells. Our study confirmed that VCR loaded STICK-NP significantly accumulated at the orthotopic brain tumor sites, and exhibited superior anti-cancer efficacy in orthotopic diffuse intrinsic pontine glioma (DIPG), the most deadly pediatric CNS tumor, then free VCR or Liposomal VCR with limited systemic toxicity. STICK-NP addresses multiple challenges for CNS tumor treatment and exhibits great potential to be translated into an effective theranostic nano-platform which could be seamlessly integrated into standard human brain tumor management (imaging-guided drug delivery) with reduced long term toxicity.

4. PERIPHERAL BLOOD FROM RELAPSED AND REFRACTORY NEUROBLASTOMA PATIENTS TREATED WITH INTERNALIZED 131I-MIBG INDICATES TIME-DEPENDENT BIOMARKERS OF EXPOSURE OUT TO 15 DAYS

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131I-metaiodobenzylguanidine (131I-mIBG) is a currently administered radionuclide developed for patients with high-risk neuroblastoma, the most common extracranial pediatric cancer. We have previously demonstrated that peripheral blood from these patients and subsequent gene expression analysis can be used to estimate internalized ionizing radiation (IR) exposure up to 96 hours after treatment. We now expand upon these studies and characterize a biodosimetery panel of transcripts with differences that persist up to 15 days after treatment. Total lymphocyte RNA from 13 patients was isolated before (untreated) or after 131I-mIBG (treated). Peripheral blood was drawn at 72 hours and 15 days post 131I-mIBG treatment. Several transcripts predictive of the early time point (72 hours) returned to baseline levels by day 15, however, several transcripts continued to fluctuate. Overall, 13 transcripts were differentially expressed at 72 hours, with CDKN1A ($p<0.000001$), FDXR ($p<0.000001$), and DDB2 ($p<0.000001$) displaying the highest up-regulation and with log2 fold changes of 2.93, 2.85, and 2.28, respectively. At 15 days post-131I-mIBG treatment, 11 of the 17 selected transcripts were differentially expressed, including XPC, STAT5B, MDM2, and IGF1R displaying significant up-regulation at 72 hours and significant down-regulation at 15 days. Interestingly, transcripts BCL2 ($p<0.0026$), PRKDC ($p<0.0015$), POLH ($p<0.0008$), and SGK1 ($p<0.0093$) were only differentially expressed at 15 days. We then utilized partial-least squares discriminate analysis (PLS-DA) and leave-one-out cross-validation to determine the specificity of exposure prediction at 15 days compared to untreated controls. Our panel was able to differentiate exposed from unexposed with 100% sensitivity and 91% specificity at 15 days, while IGF1R and SESN1 alone could predict exposure with 82% sensitivity and 91% specificity. These results suggest that transcript levels for cellular stress, including DNA damage and DNA repair, are still changing by 15 days post 131I exposure. Our studies highlight our biodosimetry transcript panel as a predictive biomarker tool for early and late internalized 131I exposures. It also demonstrates the utility of our transcript panel to differentiate exposed from non-exposed individuals out to 15 days.

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5. MITOCHONDRIA AS A THERAPEUTIC TARGET IN THE METABOLIC REPROGRAMING OF GLIOBLASTOMA (GBM)

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[2]*Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California, Davis*

Glioblastoma (GBM) is the most common yet incurable brain cancer that comprises 50% of new brain cancer cases diagnosed every year. According to the widely accepted 'Stem cell hypothesis' the primary driver of GBM tumorigenesis and progression is a small population of glioblastoma stem-like cells (GSCs). While the differentiated bulk glioblastoma cells (d-GCs) respond initially to the standard of care (SoC) treatment of temozolomide (TMZ) and radiation therapy, the GSCs are radiation and chemotherapy resistant and can repopulate the tumor-bed with their infinite self-renewal property. Currently there is no FDA-approved GSC-targeted therapy in the clinic. Our studies utilizing in vitro patient-derived GSC model demonstrate that GSCs undergo metabolic reprogramming and have 2-fold lower mitochondrial function than d-GCs, and inhibiting mitochondrial oxidative phosphorylation (mtOxphos) in vitro preferentially eliminates GSCs 500-fold more potently than the SoC chemotherapy TMZ. The mechanism by which mitochondrial inhibitors trigger GBMSC death is the intrinsic apoptosis pathway. Furthermore, using the drug repurposing strategy we identified three FDA-approved drugs pyrvinium pamoate, trifluoperazine and mitoxantrone, that killed GSCs selectively in vitro. Among the three drugs pyrvinium showed the highest selectivity and this human-approved drug could be a viable candidate for GBM adjuvant therapy. It has been reported that the cancer cells that undergo high aerobic glycolysis can utilize lactate as a substrate for ATP synthesis via mtOxphos. Hence, combining the mitochondrial inhibitors with the conventional and/or novel therapies that target glycolysis and lactate production can be advantageous in treating GBM and improving the patient prognosis.

BLOCK A4 12:10–12:45PM

1. FLUORESCENCE LIFETIME IMAGING FOR INTRAOPERATIVE DELENATION OF ORAL AND OROPHARYNGEAL CANCERS

Brent W Weyers[1], *Mark Marsden*[1], *Takanori Fukazawa*[1], *Tianchen Sun*[1], *Julien Bec*[1], *Andrew C. Birkeland*[2], *Regina F. Gandour-Edwards*[3], *Arnaud F. Bewley*[2], *Marianne Abouyared*[2], *Athena K. Tam*[1], *D. Gregory Farwell*[2], *Laura Marcu*[1]
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Oral cavity and oropharyngeal cancer together represent 3.0% of all new cancer cases, are associated with a 65.3% survivability after 5 years from initial onset, and afflict approximately 53,000 individuals annually in the United States. Adequate intraoperative delineation of cancer is the key factor for long-term survival of patients diagnosed with oral cavity and oropharyngeal cancer. The traditional gold standard for intraoperative oral and oropharyngeal cancer delineation includes white light visualization, tactile feedback, and pathologic consultation, including frozen-section histopathology. A number of limitations however are associated with these conventional diagnostic methods, motivating the development of new technology which aids in cancer margin discrimination.

Using a custom-built, fiber-based, point-scanning FLIM system to perform real-time intraoperative cancer assessments for forty patients undergoing upper aerodigestive oncologic surgery at the UC Davis Medical Center (UCDMC), we show that cancer can be resolved from healthy tissue ($p<0.001$ via Wilcoxon Rank Sum

significance testing) on the basis of autofluorescence lifetime and intensity parameters both in vivo and ex vivo, irrespective of anatomical location or cancer type. By taking advantage of alterations in tissue structural and metabolic characteristics associated with neoplastic processes, we believe our method derives FLIm-based contrast between healthy tissue and cancer on the basis of enzyme cofactors involved in cellular metabolism (e.g. NAD(P)H and FAD) as well as pathology-induced changes to matrix protein (collagen and elastin) architecture and composition.

Each spectroscopic point where FLIm data is acquired gives rise to a multiplicity of FLIm-derived metrics for analysis (e.g. lifetime, intensity, and fitting parameters) from four spectral channels, designed to resolve autofluorescence predominantly from collagen, NAD(P)H, FAD, and porphyrins. From the forty patients evaluated, we show that a combination of FLIm-derived lifetime and intensity ratio parameters can be used to train machine learning methods to aid in diagnostic decision-making. Random Forests classifiers were found to achieve superior discrimination of cancer and healthy tissue for intraoperative in vivo scans, with a mean ROC-AUC of 0.79 ± 0.08 observed. When used in an intraoperative setting, the proposed FLIm-based method provides accurate, non-invasive, real-time discrimination of tissue conditions and thus demonstrates strong potential for cancer margin assessment.

2. HYBRID NANOPLASMONIC SCAFFOLD REVEALS THE IMPORTANCE OF THE GLYCOCALYX IN LIQUID BIOPSY DIAGNOSTICS USING EXTRACELLULAR VESICLES

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Introduction/background: For more effective early stage cancer diagnostics, there is a need to develop sensitive and specific, non- or minimally invasive, and cost-effective methods for identifying circulating nanoscale extracellular vesicles (EVs). Here we report the utilization of a simple plasmonic scaffold comprised of a microscale biosilicate substrate embedded with silver nanoparticles for surface-enhanced Raman scattering (SERS) analysis of ovarian and endometrial cancer EVs. Compared to typical state-of-the-art SERS substrates, ours are rapidly and inexpensively produced without any complex equipment or lithography.

Methods: We extensively characterized the substrates with electron microscopy and developed a reproducible methodology for their use in analyzing EVs from in vitro and in vivo biofluids. Following isolation of EVs from whole blood of ovarian and endometrial cancer patients, and controls, we report effective chemical treatments for (i) decoration of metal surfaces with cysteamine to non-specifically pull down EVs to SERS hotspots, and (ii) enzymatic cleavage of extraluminal moieties at the surface of EVs that prevent localization of relevant chemical features (lipids/proteins) to the vicinity of the metal enhanced fields. We also report a methodology for tackling the inherent heterogenous structure of the scaffolds using rigorous multivariate data analysis steps in order to reproducibly reveal the cancerous SERS spectra features in the measured data sets.

Results: As SERS spectral analyses demonstrate, we successfully investigated and characterized EVs from in vitro cell cultures and clinical samples with an estimated LOD of ~600 EVs/mL. Our initial hypothesis was that enzymatic treatment of EVs would better expose the intraluminal components of EVs for SERS amplification, since SERS is a heavily distance dependent phenomena (working primarily when the molecules to detect are within a few nanometer from the metal surface). Our reasoning was that the glycoprotein component coating the EVs was “in the way” of effective SERS detection of the lipids and intraluminal components comprising single EVs (Figure 1). Instead, we found that following enzymatic treatment, the potential to distinguish cancer vs. control samples majorly decreased. We utilized linear discriminate analysis (LDA) to generate a confusion matrix to assess the accuracy, sensitivity, and specificity of detecting cancer using our SERS approach to measure clinical EVs. Compared to

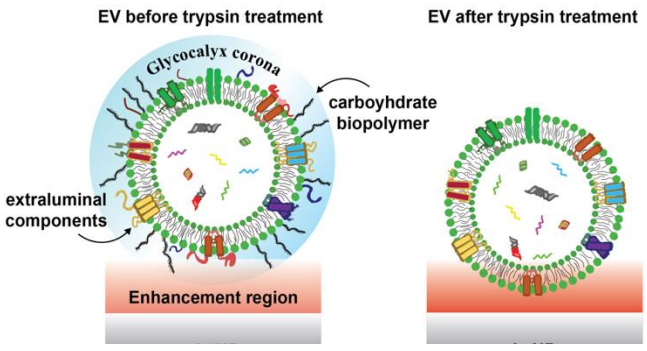

Figure 1

histopathology analysis, SERS analysis of native EVs yielded a sensitivity, specificity, and accuracy of 100%, 99.2%, and 99.4% respectively. After enzymatic cleavage of the glycocalyx for those same samples, the sensitivity dropped to 45%, specificity to 99.1%, and accuracy to 86.4%.

Conclusion: We demonstrate that SERS techniques represent an ideal tool to assess and measure the high heterogeneity of EVs isolated from clinical samples in an inexpensive, rapid, and label-free assay. Notably, we observe a major loss of sensitivity for ovarian and endometrial cancer following enzymatic cleavage of EVs' extraluminal domain, suggesting its critical significance for diagnostic platforms. While well accepted that variations in cell surface glycoproteins significantly impact the progression of cancer, the extraluminal components of EVs are not well studied. Future work from this team will include functional and analytical studies to elucidate the particular glycoproteins that are involved in distinguishing clinical samples from one another, and to discern their potential role in EV signaling in cancer.

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3. ABSORBED DOSE ASSESSMENT IN 90Y RADIOEMBOLIZATION PATIENTS: A COMPARAISON BETWEEN TOTAL-BODY PET EXPLORER AND CONVENTIONAL PET IMAGING

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Aim/Introduction: Radioembolization based on the selective delivery of 90Y microspheres to liver tumors through hepatic artery branches is an established radionuclide therapy, limited by the poor accuracy of current methods to verify dose delivery. Despite the difficulties of measuring and quantifying the very low branching ratio of 90Y positron emission (32 ppm) [1], 90Y positron emission tomography (PET) can be used for therapy evaluation to estimate the absorbed dose [2] in the liver/tumor using Monte Carlo simulations.

Materials and Methods: The patient presented here received three injections of 90Y microspheres (Theraspheres, BTG) with a total activity of 3.363 GBq and was scanned on both the total-body PET scanner uEXPLORER (United Imaging Healthcare) and the mCT Biograph (Siemens) five hours after injection. The dose distribution was estimated using Monte Carlo simulations (GATE 9.0), in which PET images were used as the activity distribution (source) and the computed tomography (CT) images described the tissue properties and anatomy. Volumes of interest (VOI) were created as image masks. In one case the masks were created from the uEXPLORER CT image and co-registered. In a second method, masks were created based on both uEXPLORER and mCT PET images and co-registered. These VOIs were overlaid with both the source images to force primary events to be generated only inside the VOI, and with the output dose-map to estimate the absorbed dose.

Results: The number of counts obtained in the VOIs was significantly higher (up to 35.1%) on uEXPLORER as a result of its higher sensitivity. Estimated absorbed doses with the uEXPLORER CT-based VOI were approximately the same with 275.02 +- 0.83 % Gy and 275.34 +- 0.92 % Gy (0.1 % difference) for uEXPLORER and mCT simulations, respectively. When two different VOIs were drawn based on the PET images, absorbed doses with uEXPLORER mask were 223.2 Gy and 230.7 Gy (3.2 % difference) for uEXPLORER and mCT simulations, respectively, while the values with mCT's mask were 247.5 Gy and 260.6 Gy (5.0 %).

Conclusion: GATE simulations showed promising results to estimate the absorbed dose from PET images. The proper definition of the VOIs is critical to conduct a comparative study. This study showed that when the VOI is based in only one CT image, the absorbed doses were the same indicating similar values of mass. On the other hand, when two VOIs were created the simulations showed different values with uEXPLORER and mCT masks. Furthermore, it is equally important to accurately identify the volumes where primary events occur, while keeping noise and artefacts to a minimum. Further studies will be conducted to assess the impact of noise and artefacts on absorbed dose estimation.

References:
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2 - Sarrut, David et al. “A review of the use and potential of the GATE Monte Carlo simulation code for radiation therapy and dosimetry applications.” Medical Physics 41 (2014)

4. THE EXPANSION OF THE ONE-BEAD-ONE-COMPOUND COMBINATORIAL CHEMISTRY TOOLBOX

Lucas Solano[1], Kellie Weeks[1,2], Kit S. Lam[1]
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The “one-bead-one-compound” (OBOC) combinatorial library methods were originally developed by Dr. Lam in 1990. This powerful combinatorial technology has resulted in the development of peptide-based cancer targeting ligands and affinity elements for efficient site-specific ligation of immunoglobulins. The advancement of chemical synthesis, encoding, and screening for this methodology continues to be explored in Dr. Lam’s lab. In this regard, we have expanded the OBOC toolbox to include Suzuki cross-coupling reactions. The Suzuki reaction is an important carbon-carbon bond forming reaction that takes place between two coupling partners, a boronic acid and an organohalide, in the presence a palladium catalyst. Suzuki coupling is the most commonly used cross-coupling reaction for the manufacturing of pharmaceuticals. The significance of the Suzuki and other cross coupling reactions resulted in the Nobel Prize in Chemistry in 2010. Here, we present the development of boronic acid-anchored, Suzuki coupling on solid support for use in encoded OBOC small molecule libraries.

5. LIVER SEGMENTATION IN CT SCANS OF PATIENTS WITH LIVER CANCER

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Radioembolization is an internal radiation therapy procedure used to treat patients with liver cancer. This process involves injecting patients with small yttrium Y-90 glass or resin beads in the hepatic artery that travel based on injection location and overall blood flow. These beads deliver targeted radiation to cancer cells, and consequently, shrinks them and lessens their adverse effects. The beads are transported by the blood; therefore knowing the blood flow in the hepatic arteries will help us predict where the Y-90 microspheres travel and cluster in the liver tumors and nontumoral regions. The blood flow simulation we have developed takes a lengthy amount of time, not compatible with the clinical requirement for a swift treatment planning. We investigate the use of machine learning as a solution to help predict blood flow. Thus, our objective is look at CT scans of patients with liver cancer and segment the liver from the entire cross section, so it becomes a basis for our neural network to learn from. Providing the machine learning algorithm with more information will allow it to better identify the liver in CT scans and eventually segment the liver more accurately.

The approach to solve this problem is to generate the information to feed a neural network which will output the location and shape of the liver to help predict blood flow in the future. We chose 10 patients as an initial sample size and began to dissect each cross section by manually outlining the liver in CT scans using the software Horos. The abdominal CT scans consisted of 33 to 270 slices for each patient. This, process provided us the general size and location of the liver in each cross section. Horos was also used to sort out the hundreds of regions that were traced out for all patients and create a training database for the machine learning program.

The significance of information that can be gained from possible results is far-reaching. Research in this field can help patients receive a more efficient treatment and improve the survival of liver cancer patients treated with radioembolization. This blood flow simulation can also be used in other applications such as chemoembolization to help predict the distribution of the therapeutic beads. This swift method may aid in getting many the help they need faster than a previous, unoptimized method. The work presented here focuses on liver segmentation, which is an important initial step of hepatic blood flow simulation.

BLOCK A5 12:50 - 1:25PM

1. A CRISPR SCREEN TO EXPANDING THE THERAPEUTIC ATLAS FOR CANCER TREATMENT

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[1]UC Davis Genome Center, [2] Comprehensive Cancer Center, and [3]Departments of Medical Microbiology, Microbiology and Molecular Genetics [4]Biochemistry and Molecular Medicine

The repertoire of actionable targets for most cancers is limited. To expand this repertoire, genome-wide screens have been used for decades. However, most of these screens have focused on gene inactivation strategies such as ENU mutagenesis, gene-trap, RNAi, and Cas9 nucleases. These screens have identified many genetic “dependencies” and “addictions.” Yet most of these screens have failed to identify a third class of tumor actionable targets that we are calling “epigenetically dormant tumor suppressor” genes. We hypothesize that cancers display specific sensitivity to unique classes of dormant genes whose function leads to anticancer activities. Our goal is to identify and prioritize dormant genes based on their inhibitory functions in breast cancer using CRISPR activation (CRISPRa). CRISPRa is based on tethering transcriptional activation domains to a nuclease-dead Cas9 protein (dCas9) and pairing this with guide RNA libraries for genome-wide screens. We have carried out “proof-of-concept” experiments in breast cancer cell lines and identified known and novel genes whose activation leads to cell growth repression. Here, we will present our experimental approach, the first set of bioinformatic analyses, and highlighting genes for validation and future exploration. By utilizing the CRISPRa screening platform, combined with straight forward tissue culture experiments and bioinformatics pipelines, scalable genetic therapeutic targets can be identified for cancer treatment.

Funding: NIH T32 in Oncogenic Signals and Chromosome Biology (J.A.G.)
This work was supported in part by gift funds from the UC Davis Comprehensive Cancer Center (D.J.S and C.S.)

2. INCIDENCE OF BREAKTHROUGH FUNGAL INFECTIONS WITH ISAVUCONAZOLE VERSUS POSACONAZOLE PROPHYLAXIS IN AMP PATIENTS

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Background: Patients with acute myeloid leukemia (AML) are at increased risk of developing fungal infections, particularly after intensive chemotherapy.1 Posaconazole is the only category 1 recommended antifungal prophylaxis agent in this setting.2 Posaconazole’s strong CYP enzyme inhibition lends unfavorability with respect to drug-drug interactions, particularly with new small-molecule targeted therapies in AML, such as venetoclax.2-5 Isavuconazole has increasingly been used for antifungal prophylaxis in AML patients due to only demonstrating moderate CYP enzyme inhibition and subsequently less severe drug-drug interactions.6 Current guidelines do not recommend the use of isavuconazole given the limited information regarding its efficacy in this setting, warranting further research.2, 7

Methods: In this retrospective, single-center cohort study, adult patients with AML who were consecutively treated between 1/2014 and 10/2019 were evaluated during the period of induction and salvage chemotherapy. The subjects were divided into two cohorts based on antifungal agent used for prophylaxis: isavuconazole versus posaconazole. Breakthrough fungal infections were assessed using the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) criteria. Pediatric patients and patients deemed to be from a vulnerable population (i.e. prisoners, pregnant, study site employees) were excluded. The primary endpoint was the incidence of proven/probable BTFI in each cohort. Statistical analysis included Fisher’s exact test, chi-squared analysis, and Wilcoxon two-sample test, where appropriate.

Results: 132 patients were included for analysis (n=66 in each cohort). The isavuconazole cohort was older (mean age 64.5 years vs 52.8 years; p<0.001) and had a larger proportion of low-intensity AML therapy (71%

vs 5%; p <0.001). The incidence of BTFI was similar between the isavuconazole and posaconazole cohorts (7.6% vs 4.5%; p=0.758). In those with a BTFI, mortality rate attributed to infection was similar between the cohorts (40% vs 33%; p>0.999).

Conclusion: Isavuconazole is a reasonable option for antifungal prophylaxis in patients with AML, though consideration may be given to limit its use to situations where avoidance of strong CYP inhibition is necessary.

3. NUCLEAR RECEPTOR ROR-Γ AND KINASE PBK DRIVE A FEED-FORWARD LOOP IN HYPERACTIVATING AR SIGNALING IN MCRPC

Xiong Zhang[1], Zenghong Huang[1], Jin Li[1], Christopher P. Evans[2], Hong-Wu Chen[1]
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Metastatic castration-resistant prostate cancers (mCRPCs) are often highly aggressive diseases with few therapeutic options. Hyperactivation of androgen receptor (AR) signaling is thought to be the central factor that drives CRPC progression. However, AR signaling network in mCRPC remains to be investigated. In our previous study, we identified nuclear receptor Retinoic acid-related orphan receptor gamma (ROR-γ) as a novel key driver of AR gene overexpression and signaling. In this study, we found that ROR-γ could promote CRPC cell migration and invasion as well as proliferation. Through RNA-seq and ChIP-seq analysis, we identified PDZ binding kinase (PBK), a serine/threonine kinase, as a novel downstream gene of ROR-γ to exert the cellular effects. We found that whereas the expression of PBK is low in benign tissue, it increases significantly in mCRPC tumors and correlates with Gleason scores. Alteration of ROR-γ expression significantly down- or up-regulated the mRNA and protein level of PBK. Co-IP and protein degradation assay revealed that ROR-γ, AR and PBK formed a feed-forward loop in mCRPC cells. We also found that ROR-γ and AR could bind to the regulatory region of PBK gene to drive its expression and that elevated PBK protein could associate with ROR-γ and AR to stabilize their protein functions. We believe that this feedforward loop led to a sustained hyperactivation of AR and ROR-γ signaling, as dual inhibition of PBK and ROR-γ synergistically inhibited ROR-γ and AR expression, resulting in a dramatically suppression of CRPC cell growth. Therefore, our study provided a promising, new strategy for treatment of advanced forms of prostate cancer.
Funding: This work was supported in part by the Prostate Cancer Foundation (PCF) Challenge Award, grants from NIH (R01CA206222) and the US Department of Defense (PC150758), and by the UC Davis Comprehensive Cancer Center.

4. INDUCTION OF BRCA2 INSUFFICIENCY, GENOME INSTABILITY AND TUMORIGENESIS BY SYCP3

Ash Jay[1,2], Sumit Sandhu[1,2], Hang Phuong Le[2], Jie Liu[2], Alexander Borowsky[3,4], Neil Hunter[2,4], Wolf-Dietrich Heyer[2,4]
[1]Both authors contribute equally to this project [2]*Department of Microbiology and Molecular Genetics,* [3]*Department of Pathology and Laboratory Medicine,* [4]*UC Davis Comprehensive Cancer Center. University of California, Davis*

Homologous recombination (HR) is a template-dependent high-fidelity pathway that functions to accurately repair DNA damage and thereby helps maintain genome integrity. Loss of HR in somatic cells leads to genomic instability and tumorigenesis; whereas in germ cells it leads to de-novo mutation, aneuploidy, miscarriages, and infertility. Breast cancer susceptibility protein, BRCA2 plays a central role in regulating HR. BRCA2 localizes to the site of DNA damage and recruits RAD51 in somatic cells and both RAD51 and DMC1 in meiotic cells, to nucleate filaments of these proteins on DNA ends. The RAD51/DMC1 nucleoprotein filaments function in the two signature steps of HR: 1) homology search for a DNA template and 2) DNA strand invasion. Loss of BRCA2 function is associated with increased risk of breast, ovarian and other cancers. SYCP3 is an essential structural component of the meiosis-specific synaptonemal complex. It is typically expressed only in germline cells (i.e. in testis and ovary) but not in somatic cells. However, emerging evidence indicates that SYCP3 is mis expressed in certain cancer cells and primary tumors, and hence SYCP3 has been termed a cancer/testis antigen. Recently, it was reported that in somatic cells SYCP3 interacts with BRCA2 and impairs recruitment of RAD51. The structural role of SYCP3 in meiosis is relatively well

understood, but its potential direct role in HR and effects in somatic cells remain unclear. Our research addresses how SYCP3 regulates BRCA2 function in germline and somatic cells.

First, we evaluate SYCP3 protein expression in breast cancers using immunohistochemistry (IHC). The published studies that evaluate SCYP3 misexpression in cancers are based on RNA transcript analysis which may not be correlative or indicative of SYCP3 protein levels. Our preliminary results indicate significantly higher expression of SYCP3 in cancers with poorer prognosis.

Next, we establish the biochemical mechanism by which SYCP3 leads to functional loss of HR in somatic cells by in vitro assays using purified proteins. Our results indicate direct interaction between SYCP3 and BRCA2 which impairs the BRCA2-RAD51 interaction. SYCP3 also interacts with RAD51 and impairs RAD51-mediated strand invasion in the absence of BRCA2. However, the presence of another essential recombination protein, RAD54, appears to attenuate the disruption of HR which raises concerns about the biological significance of this BRCA2-indepdnent effect.

Given that BRCA2 and SYCP3 interact in cancer cells, we speculate that this interaction may be functional under normal physiological conditions, i.e. in cells undergoing meiosis. Our project also aims to dissect importance of BRCA2-SYCP3 interaction during meiosis. We used CRISPR/Cas9 to generate the first viable tagged allele of Brca2 in mice, Brca2-3HA. These mice are viable and fertile and give us opportunity to investigate BRCA2 dynamics during meiosis, which has not been possible with commercially available BRCA2 antibodies. So far, our data indicate that BRCA2 localizes to recombination sites along with other key factors, such as RAD51. However, meiotic localization of BRCA2 is highly dependent on SYCP3, as BRCA2-3HA immunostaining foci are not detectable in Sycp3 mutant spermatocytes. These data point to an intimate relationship between SYCP3 and BRCA2 during meiotic recombination that is expected to shed light on the pathology of SYCP3 expression in cancer cells.

Together, our studies will establish how SYCP3 expression in somatic cells interferes with BRCA2-dependent HR.

Acknowledgements: The support through seed funds from the UC Davis Comprehensive Cancer Center is gratefully acknowledged.

BLOCK B1 12:50 - 1:25PM

1. ESTIMATING SMOKING MISMEASUREMENT, MISSAMPLING, MISPERCEIVED RISKS, AND RESIDUAL CONFOUNDING IN COHORT STUDIES OF UNITED STATES (US) LUNG CANCER MORTALITY

Bruce Leistikow, MD, MS
UCD, Public Health Sciences, retiree

Background: Cohort studies' (cohorts') "conservative" smoking mismeasurement/misreporting, missampling/volunteer, ... biases are clear but largely unquantified factors in cohort-related: residual confounding; spurious associations; and resulting "everything causes cancer" risk misperceptions that perpetuate smoking deaths epidemics.

Objectives: Estimate effects of those biases on prominent cohort-based estimates of lung cancer smoking-attributable (SA) age standardized mortality rates (ASMRs) and relative risks (RRs).
Methods. We contrasted cohorts' versus semi-experimental ("~observed" staggered exposure, ...) SA ASMRs given the latter's consistency and resulting expert consensus that staggered cigarette smoking epidemics drove subsequent staggered lung cancer epidemic ASMRs. We estimated the lung cancer ASMRs and RRs of the: 1. Truly unexposed based on exponential back-extrapolation from 1915-1945 English men, 1930-1945 US women, and other ASMRs; 2. The recent US based on CDC versus published Global Burden of Disease, 2014 Surgeon General's Report, and similar prominent cohort "never smoker" (referent) plus SA lung cancer ASMRs or counts;

Results: ~Observed US male lung cancer ASMRs (all in deaths/100,000) and RR ranged from 1 (sensitivity range (SR) 0.25-4) in the unexposed and 44 in 2017 to 73 in 2000-4 overall versus the various cohorts' ASMRs of 7 to 21 in referents and 42-51 overall. The cohorts overlooked 89-92% (SR 57-99%) of the male ~observed lung cancer RR, but less absolute risk. Females were similar.

Conclusion: Cohorts probably greatly underestimate lung cancer and other, SA: 1. ASMR mostly due to volunteer bias; 2. RR mostly due to smoking in cohorts' "never smokers;" and 3. Residual confounding by mismeasured smoking.

2. ENGRAILED-1 AND EPIGENETIC VULNERABILITIES IN METASTATIC PANCREATIC CANCER

Chang-il Hwang[1], Jae Seok Roe[2], Eunjung Lee[1], Jihao Reno Xu[1], Michael Hollingsworth[3], Christopher Vakoc[2], David Tuveson[2]
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Pancreatic cancer is the most deadly disease in human malignancies and effective treatment options are limited. Here, we report that Engrailed-1 (EN1), a neuro-development transcription factor, plays a critical role in pancreatic cancer progression and metastasis via epigenetic mechanism of gene regulation by employing multi-orthogonal approaches including pancreatic organoid cultures and transplantation models. EN1 is a homeo-domain transcription factor, acting as a transcriptional repressor via recruiting transcriptional repressive complexes. EN1 is highly expressed in metastatic lesions of pancreatic cancer mouse models and patients. In addition, EN1 expression is associated with poor prognosis and the squamous molecular subtype of pancreatic cancer. We show that EN1 expression endows aggressive characteristics to pancreatic cancer cells and mirrors the signature of Kdm6a deficiency of pancreatic tumors, which has been shown to lead to squamous subtype of pancreatic tumors. Depletion of EN1 expression in metastatic pancreatic cancer cells significantly reduced the migratory and invasive characters as well as cell survival. In particular, gain- and loss-of-function approaches of EN1 revealed that EN1 is pro-metastatic factor in vivo. This study will provide a new insight how EN1-mediated epigenetic alterations impact on aggressive traits of pancreatic cancer. This may open novel avenues for the treatment of metastatic pancreatic cancer.

Chang-il Hwang is supported by NIH/NCI K22 CA226037. This work was supported in part by the UC Davis Comprehensive Cancer Center Support Grant NCI P30CA093373.

3. ONE-COMPONENT NEW-CHEMICAL-ENTITY NANOMEDICINE (ONN) TO TARGET AUTOPHAGY IN CANCERS

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Autophagy, a catabolic process which harnesses lysosomal-mediated degradation of cellular proteins and organelles to regenerate energy in the setting of metabolic stress, is associated with drug resistance to a variety of cancers. Hypoxia-induced autophagy in the tumor microenvironment activates several tumor escape mechanisms, which effectively counteract anti-tumor immune responses mediated by natural killer and cytotoxic T lymphocytes. Therefore, strategies aiming at targeting autophagy in cancer cells in combination with other therapeutic strategies have inspired significant interest to overcome immunological tolerance and promote tumor regression. Autophagy inhibition decreases ERK phosphorylation and synergizes MEK as well as ERK inhibitors for highly effective cancer treatments. Furthermore, targeting autophagy inhibits tumor growth by enhancing NK cells infiltration. In preclinical models, autophagy inhibition with chloroquine (CQ)

derivatives augments the efficacy of many anticancer therapies, but CQ has limited activity as a single agent. Clinical trials are underway combining anticancer agents with hydroxychloroquine (HCQ), but concentrations of HCQ required to inhibit autophagy are not consistently achievable in the clinic.

Integration of the unique advantages of the fields of drug discovery and drug delivery is invaluable for the advancement of drug development. Here we propose a one-component non-prodrug nanomedicine (ONN) strategy to generate self-delivering chemical entities through incorporation of the self-assembly principle into drug design. A lysosomotropic detergent (MSDH) and an autophagy inhibitor (Lys05) are hybridized to develop bisaminoquinoline derivatives that can intrinsically form nanoassemblies. The selected BAQ12 and BAQ13 ONNs are highly effective in inducing lysosomal disruption, lysosomal dysfunction and autophagy blockade and exhibit 30-fold higher antiproliferative activity than hydroxychloroquine used in clinical trials. These single-drug nanoparticles demonstrate excellent pharmacokinetic and toxicological profiles and dramatic antitumour efficacy in vivo. In addition, they are able to encapsulate and deliver additional drugs to tumour sites and are thus promising agents for autophagy inhibition-based combination therapy. Given their transdisciplinary advantages, these BAQ ONNs have enormous potential to improve cancer therapy.

FRIDAY POSTER PRESENTATIONS (ABSTRACTS)

BLOCK C1 8:00–8:35AM

1. CENTRAL VENOUS CATHETER PLACEMENT IN NEUTROPENIC PEDIATRIC ONCOLOGY PATIENTS

S.C. Stokes[1], *J.E. Jackson*[1], *C.M. Theodorou*[1], *K.J. Yamashiro*[1], *E.G. Brown*[1]
[1]*Department of Surgery, University of California-Davis*

Background: The ideal absolute neutrophil count (ANC) for placement of a tunneled central venous catheter (CVC) in pediatric oncology patients is unknown. We hypothesized that placement of CVCs in neutropenic patients is not associated with increased infectious complications.

Methods: Records of pediatric oncology patients who underwent CVC placement at a tertiary pediatric hospital from 2014-2019 were reviewed. Patients who were neutropenic (ANC <500/mm3) at the time of CVC placement were compared to those with a normal ANC. The primary outcome was catheter removal within 30 days due to central line associated blood stream infection (CLABSI). Secondary outcomes included CVC removal for CLABSI at any time.

Results: A total of 292 central venous catheter placements in 242 patients were reviewed. Overall, 3 (1.02%) CVCs were removed within 30 days due to CLABSI and 24 (8.2%) CVCs were removed at any time for CLABSI. Patients with neutropenia at the time of insertion (n=37) had an increased rate of removal within 30 days for CLABSI which approached statistical significance (5.4% vs 0.46%, p=0.057). However, this was not significant on multivariable logistic regression controlling for age, weight and type of malignancy (OR 10.43, 95% CI 0.618, 172.41). They were not at increased risk of removal for CLABSI at any time (10.8% vs 9.3%, p=0.763).

Conclusion: Neutropenia at time of placement does not increase risk of removal for CLABSI within 30 days when controlling for type of malignancy, age and weight. Neutropenia is not associated with increased risk of removal for CLABSI at any time.

2. CENTRAL VENOUS CATHETER PLACEMENT IN PEDIATRIC ONCOLOGY PATIENTS: WHAT IS THE IMPACT OF THROMBOCYTOPENIA?

S.C. Stokes, K.J. Yamashiro, C.M. Theodorou, J.E. Jackson, E.G. Brown
Department of Surgery, University of California-Davis

Background: Concerns for bleeding complications in pediatric oncology patients with thrombocytopenia can lead to increased platelet transfusions and delays in central venous catheter (CVC) placement. However, the ideal platelet threshold for CVC insertion is unknown. We hypothesized that placement of CVCs in patients with a platelet count of <50x109/L is not associated with increased risk of severe bleeding.

Methods: Records of pediatric oncology patients who underwent CVC placement at a tertiary pediatric hospital from 2014-2019 were reviewed. Patients with platelet counts above and below 50x109/L at the time of placement were compared. The primary outcome was perioperative bleeding complications, defined as intraoperative or postoperative bleeding requiring prolonged pressure or application of a hemostatic agent, or development of a hematoma. Bleeding was categorized as mild if no intervention was required, moderate if the patient required a red blood cell transfusion and severe if the patient required a massive transfusion or surgical intervention.

Results: A total of 292 CVC placements in 242 patients were reviewed. Patients with a platelet count of <50x109/L (n=22) at the time of CVC placement were at increased risk of perioperative bleeding complications (13.6% vs. 2.2%, p=0.018). This remained significant on multivariable regression controlling for age, weight, type of malignancy and pre-operative hemoglobin (OR 7.29, 95% CI 1.50-35.59). When evaluated by severity

of bleeding patients with a platelet count of <50x109/L remained more likely to have mild bleeding (13.6% vs. 1.1%, p=0.007). However, there was no difference in the rate of moderate bleeding (0% vs. 1.1%, p>0.999), and no patients experienced severe bleeding.

Conclusion: A platelet count of <50x109/L at the time of CVC insertion is associated with increased risk of perioperative bleeding complications. However, the majority of this bleeding was mild, and there was no association between a platelet count of <50x109/L and bleeding requiring intervention. It may be possible to safely lower the platelet threshold for CVC insertion.

3. ASSOCIATION BETWEEN A PROTECTIVE GENETIC VARIANT OF INDIGENOUS AMERICAN ORIGIN WITHIN THE 6Q25 REGION AND SUBTYPE-SPECIFIC BREAST CANCER RISK IN LATIN AMERICAN WOMEN

Valentina Zavala[1], Tatiana Vidaurre[2], Sandro Casavilca[2], Carlos Castañeda[2], Jeannie Vásquez[2], Fernando Valencia[2], Zaida Morante[2], Monica Calderon[2], Julio Abugattas[2], Henry Gómez[2], Hugo Fuentes[2], Ruddy Liendo Picoaga[2], Jose M. Cotrina[2], Zaida Morante[2], Fernando Valencia[2], C. Monge-Pimentel[2], Silvia Neciosup[2], Bizu Gelaye[3], Laura Fejerman[1]
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In the United states, the incidence of breast cancer in women of Latin American origin is lower compared to European American and African American women. Among Latinas, a population-specific common polymorphism in the 6q25 chromosomal region near the estrogen Receptor 1 (ESR1), gene (rs140068132A) has been associated with breast cancer risk. The G allele, which is only observed in individuals with Indigenous American Ancestry (IAA), is less common in breast cancer cases compared to unaffected controls. In the discovery genome-wide association study, the G allele was more common in estrogen receptor positive (ER+) compared to ER- patients. In this study we assessed the association of the rs140068132 polymorphism with specific breast cancer subtypes in patients with high IAA.

We genotyped 1,327 BC patients recruited at the Instituto Nacional de Enfermedades Neoplasicas in Lima, Peru, that agreed to participate in the Peruvian Genomics of Breast Cancer (PEGEN-BC) Study. Genotype data for the rs140068132 polymorphism was available for 3,338 women without a breast cancer diagnosis from a study of pregnant women (PrOMIS) from Lima, Peru. After quality controls, 1,312 cases remained. IAA and African ancestry components were estimated using ADMIXTURE v1.3. Four major breast cancer subtypes (ER/PR+ HER2-, ER/PR+ HER2+, ER/PR -HER2+, ER/PR- HER2-) were defined using immunohistochemical markers. Multinomial and binomial logistic regression analyses were performed in R including age at diagnosis, IAA and African ancestry as covariates and the ER/PR+ HER2- subtype was defined as reference.

The average age at diagnosis for the PEGEN-BC Study patients was 50 years (±10.97) and did not differ by tumor subtype. The proportion of IAA component in ER/PR+ HER2-, ER/PR+ HER2+, ER/PR-HER2+ and ER/PR- HER2- tumors was 74% (±0.18), 76% (±0.18), 79% (±0.14) and 76% (±17), respectively (p= 0.007). Fifty percent of cases were ER/PR+ HER2-, 19% ER/PR+ HER2+, 12% ER/PR-HER2+ and 15% ER/PR-HER2-. Overall, the rs140068132-G allele frequency was 14%, and varied by tumor subtype. The G allele was most common in patients with ER/PR+ HER2- tumors (16%), and less so among patients with other subtypes (12%,11% and 12%; respectively). The frequency of the rs140068132 G allele among unaffected Peruvian women from the PrOMIS study was 25%. Multinomial logistic regression models suggested that the AG genotype (vs. AA) was not only associated with reduced odds of developing ER- tumors, but also ER/PR+HER2+ tumors (OR=0.69, 95%CI 0.49-0.97, p=0.04). In a logistic regression model where ER/PR+HER2- tumors where compared to all other subtypes, the odds ratio associated with the AG genotype vs. AA was 0.64 (95%CI 0.49-0.82, p=0.0007). Additionally, we observed that the frequency of GG genotype was higher among patients with ER/PR- HER2- (3% vs.1%) tumors and overall genotype analyses were not consistent with a simple additive effect on tumor subtype for the G allele.

Our results are in line with the previously reported association between breast cancer risk and the rs140068132 polymorphism in Hispanics/Latinas. Additionally, our results strongly suggest that the

rs140068132-AG genotype is more common in patients with ER/PR+ HER2- tumors compared to other subtypes. The mechanisms leading to the observed association between this protective variant and the least aggressive ER/PR+HER2 negative breast cancer needs further investigation. The rs140068132 variant is located in an enhancer region close to ESR1, suggesting a possible role of this variant on ESR1 expression and as a result, the development or ER-positive tumors. Ongoing gene expression analyses focused on the rs140068132 polymorphism, the ESR1 gene, and other associated genes, will help to elucidate its functional significance and might lead to new approaches in breast cancer chemoprevention.

4. MALE BREAST CANCER: CHARACTERISTICS AND OUTCOMES IN CALIFORNIA, 1988 TO 2017

Frances B. Maguire[1], Brenda M. Hofer[1], Cyllene R. Morris[1], Arti Parikh-Patel[1], Candice A. Sauder[2], Theresa H.M. Keegan[1,3]
[1]California Cancer Reporting and Epidemiologic Surveillance Program, University of California Davis Comprehensive Cancer Center, University of California Davis Health [2]Division of Surgical Oncology, University of California Davis Comprehensive Cancer Center [3]Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine

Background: Male breast cancer (MBC), less than 1% of all breast cancers, has been less frequently studied than female breast cancer (FBC). Recent studies show that MBC is genetically distinct from FBC, but treatment recommendations still are based on FBC data. Therefore, a contemporary population-based study is needed to examine the characteristics and survival trends in MBC patients compared to their FBC counterparts who have experienced improved survival.

Objective: To describe characteristics and survival for MBC compared to FBC.

Methods: We obtained data from 4,848 MBC and 786,795 FBC patients diagnosed from 1988 to 2017 from the California Cancer Registry. Demographic and clinical characteristics were compared using Chi square tests. Age-adjusted mortality rates and five-year relative survival were calculated with SEER*stat, while AAPCs (average annual percent change) were calculated with Joinpoint software.

Results: More men (16.0%) were diagnosed late stage (stages III or IV) compared to women (10.7%). More men were estrogen (73.7%) and progesterone (65.3%) receptor positive (vs. 63.5%, 52.9% for women), and fewer received radiation (20.0%) compared to women (39.7%). These differences were all statistically significant ($p<0.001$). Mortality trends for men remained flat over the study period (AAPC=1.55, $p=0.43$), while for women mortality decreased (AAPC= -1.63, $p=<0.001$). Five-year relative survival was 96.9% for localized disease (vs. 98.4% for FBC) and 16.9% for distant disease (vs. 29.4% for FBC).

Conclusion: Men with breast cancer are diagnosed at later stages and have worse survival than women with breast cancer. Further research is warranted to better understand the poorer outcomes that men with breast cancer experience.

5. THE SACRAMENTO AREA BREAST IMAGING REGISTRY (SABIR): A RICH RESOURCE FOR BREAST CANCER SCREENING AND OUTCOMES RESEARCH

Olivia Sattayapiwat, MS, MPH; Michael C.S. Bissell, PhD; Evan de Bie; Yang Vang, Diana L. Miglioretti, PhD; Department of Public Health Sciences, University of California Davis School of Medicine, Davis, CA

Breast cancer screening and surveillance are rapidly changing as we realize the limitations of mammography and move towards woman-centered decision making and new breast imaging modalities. Evidence on the effectiveness of breast imaging modalities overall and for women with specific characteristics is urgently needed, which requires prospective longitudinal data collected on a very large cohort of individuals from screening through diagnosis, treatment, surveillance, and death. We created the Sacramento Regional Breast Imaging Registry (SABIR) to answer pressing questions about the best ways to provide breast cancer screening and surveillance.

The SABIR database currently includes information on 263,664 breast imaging exams, 3,132 breast cancer diagnoses, and 9,011 breast biopsies from 62,121 unique individuals. Minorities make up 30% of the population, including 10% Latinx, 9% Asian, and 7% Black. Individuals with breast imaging exams have been linked to the California Cancer Registry for complete capture of breast cancer diagnoses; to California vital statistics for complete capture of deaths; to the UC Davis Comprehensive Cancer electronic medical records for detailed capture of breast cancer treatment; and to UC Davis medical records for capture of COVID diagnoses, primary care visits for breast symptoms, and comorbidities.

SABIR is being leveraged for many research studies. In collaboration with the Breast Cancer Surveillance Consortium (BCSC), we were awarded funding from the Patient Centered Outcomes Research Institute (PCORI) to develop a toolkit for breast imaging facilities to prioritize women for breast imaging and biopsy services during periods of reduced capacity and messaging content to address women's perceived barriers to receiving breast imaging services during the COVID-19 pandemic. With funding from the UC Davis Center for Health Policy Research, we are evaluating changes in breast imaging utilization and timeliness of care during COVID-19. Another study is examining potential racial disparities that could arise due to breast density notification laws, which only require reporting of breast density and not other risk factors associated with poor screening mammography outcomes. Another study is investigating patient- and facility-level factors that contribute to delays in breast biopsy following a positive mammogram, with a particular focus on the impact of racial/ethnic, socio-economic, and rural/urban disparities. SABIR is also a great resource for students and early-stage investigators. For example, SABIR is being used for a PhD dissertation focused on improving breast cancer risk prediction by incorporating more detailed information on benign breast diagnoses.

We are continuing to expand the SABIR database by mapping information collected in clinical practice to variables needed for impactful research. Our research utilizing SABIR will improve the care of women undergoing screening mammography and individuals with breast cancer by helping facilities prioritize breast imaging services, developing communication tools to help women feel comfortable receiving breast imaging services during COVID-19, identifiying reasons for disparities in breast imaging care, improving breast cancer risk prediction models, and developing more personalized screening and surveillance strategies.

Acknowledgements: The collection of SABIR data was supported by the UC Davis Comprehensive Cancer Center, the Placer County Breast Cancer Foundation, and the UC Davis Clinical and Translational Science Center.

BLOCK C2 8:00–8:35AM

1. PHASE I/II TRIAL OF BMS-986205 AND NIVOLUMAB AS FIRST LINE THERAPY IN HEPATOCELLULAR CARCINOMA

Jasmine Huynh, MD, Jingran Ji, MD, Justin Chen, MD, May Cho, MD, Arta M Monjazeb, MD, Sepideh Gholami, MD, Kit Tam, MD, Steven Colquhoun, MD, Souvik Sarkar, MD, Eric Chak, MD, Christopher Bowlus, MD, Catherine Vu, MD, John McGahan, MD, Michael Corwin, MD, Ghaneh Fananapazir, MD, Susan Stewart, PhD, Edward Kim, MD
University of California, Davis, CA

Background: Hepatocellular carcinoma (HCC) is the leading cause of cancer-related death worldwide and US and incidence of HCC is rising and estimated 782,000 new cases per year worldwide. The first line systemic therapy for advanced disease is sorafenib with a moderate overall survival (OS) of three months over supportive care. More recently, several additional agents have been approved. Lenvatinib was approved based on a non-inferiority trial comparing it to sorafenib. Nivolumab was also approved as second line therapy in patients with unresectable HCC refractory to sorafenib. BMS-986205 (FLX287 or F-1287) potently and selectively inhibits human Indoleamine-2,3- dioxygenase 1 (IDO1) with no activity against another tryptophan degradation enzyme, tryptophan 2,3-dioxygenase (TDO). IDO is an intracellular enzyme expressed by numerous human malignancies, including HCC, and has been shown to play a central role in orchestrating

immune suppression within the tumor microenvironment (TME). Preliminary data in bladder and cervical cancers have shown objective response and safety data support a dose of 100mg daily.

Methods: This is a phase I/II study using a Simon optimal two stage design for efficacy of BMS-986205 in combination with fixed dose IV nivolumab, with phase 1 being dose escalation of BMS-986205 with nivolumab and phase 2 being an open-label expansion in patients with HCC. Our primary objectives include obtaining the safety and tolerability of BMS-986205 in combination with nivolumab in unresectable/metastatic HCC and determining efficacy as defined by objective response rate (ORR) of BMS-986205 used with nivolumab in unresectable/metastatic HCC in the first line setting. Secondary objectives include obtaining preliminary data on disease control rate (DCR), duration of response (DOR), ORR, progression free survival (PFS), and overall survival (OS) of BMS-986205 in combination with Nivolumab in unresectable HCC. We also aim to further evaluate safety of therapy unresectable HCC.

Our primary inclusion criteria were: 1) histologically or imaging confirmed hepatocellular carcinoma, disease that is not amenable for curative treatment approach. 2) measurable disease based on RECIST v1.1. 3) ≥1 liver lesions accessible for core biopsy that was either not previously treated by liver-directed therapy or progressed following liver-directed therapy. 3) Child-Pugh score of A. 4) ECOG performance status of 0 or 1.

Our primary exclusion criteria were: 1) Previous or current systemic cancer-related therapy. 2) Immunodeficiency or active autoimmune disease or recent steroid/ immunossuppresive therapy 3) Clinically significant ascites. 4) Hepatic encephalopathy. 5) Liver directed therapy ≤4 weeks before the first dose of study. 6) History of esophageal or gastric variceal bleeding within 3 months of study.

The estimated study duration is 36 months with a 24 month accrual period. All patients will be followed for 100 days after the last dose of treatment or until all treatment related clinically significant toxicities resolve to baseline or grade ≤ 1.

Results: The study is currently ongoing in the Phase I dose escalation phase with six patients accrued so far.

2. HEPATOCELLULAR CARCINOMA TREATMENT USING A GALECTIN 1 INHIBITOR

Tsung-Chieh Shih[1], *Ying Hu*[2]*, *Ruiwu Liu*[1], *Kit Lam*[1], *Yu-Jui Yvonne Wan*[2]
[1] *Department of Biochemistry and Molecular Medicine,* [2] *Department of Pathology and Laboratory Medicine, University of California, Davis, Sacramento, California, USA.*

The incidence of hepatocellular carcinoma (HCC) has been increasing for decades. Although surgical interventions and locoregional therapy are available options, up to 80% of patients present with advanced disease not amenable to standard therapies. There is an urgent need to develop alternative treatments and combination therapies. Galectin-1 (Gal1) binds to β-galactoside-containing glycoconjugates. Gal1 can bind RAS, integrins, laminins, etc. Due to its overexpression in cancer, Gal1 is a viable target for many types of cancer including liver. The level of Gal1 is positively correlated with a negative outcome of sorafenib treatment. In this study, we examined the expression of Gal1 in human and mouse HCCs. We also studied the effect of a Gal1 inhibitor named LLS30 in HCC treatment for the first time. After analyzing the TCGA data, we saw overexpression of Gal1 in human HCCs (n=370) in comparison with normal livers (n=50). Moreover, elevated Gal1 was associated with poor overall survival. Immunohistochemistry staining revealed elevated Gal1 in stroma and tumors. Moreover, there was a negative correlation between Gal1 expression and tumor purity, i.e., percentage of malignant cells in HCCs, indicating the presence of Gal1 in tumor microenvironment rather than tumor itself.

Gal1 secretion is evidenced by detection of Gal1 in a conditioned medium of human liver cancer Huh7 and HepG2 cells, which could be reduced by Gal1-siRNA. Additionally, recombinant Gal1 induced apoptosis of human peripheral blood mononuclear cells and LLS30 prevented apoptosis. In vivo HCC treatment using LLS30 was conducted in orthotopic HCC mouse models. Six-week-old FVB/N mice were injected hydrodynamically with myr-AKT1 and NRasV12 along with sleeping beauty transposase to generate HCC. Seven days after tumor initiation, one group of mice were euthanized to obtain pretreatment information, which showed the liver-to-body weight ratio was doubled (9% vs. 4.5% in healthy mice). Another two groups received

either vehicle or LLS30 (50 mg/kg, daily iv) and were killed 14 days later. In the vehicle-treated mice, the liver-to-body weight ratio continued rising and reached 18%. However, in LLS30-treated mice, the ratio was 12%, 33% less than untreated groups. Additionally, the development of HCC was accompanied by splenomegaly, but there was no difference in spleen weight between LLS30-treated mice and the pretreated group. Moreover, based on total blood count, compared with untreated mice, LLS30 treatment did not alter hemoglobin, red cell distribution width, mean corpuscular volume, hematocrit, platelets, red blood cells, or various white blood cells. No other apparent toxicity of LLS30 was noted in HCC-bearing mice. The mechanism by which LLS30 treats HCC is under investigation. Because Gal1 expression in human HCC is positively associated with PD1 level, the next step is to exam whether LLS30 can improve the immunotherapeutic effect of anti-PD1. Together, the generated data so far suggests that inhibiting Gal1 targets tumor microenvironment and is effective to treat HCC in orthoptic mouse models generated in immunocompetent mice.

Acknowledgement: This study is in part supported by an Immuno-Oncology Initiative Pilot Grant provided by the UCD Comprehensive Cancer Center.

3. PROMOTING 'ADAPTIVE' NK CELL RESPONSE IN HEMATOLOGIC CANCERS

Joshua Meckler[1], *Gustavo A. Barisone*[1,3], *Daniel Vang*[1], *William Murphy*[1,2,3], *Joseph Tuscano*[1,3]
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There has tremendous success and enthusiasm for cancer immunotherapy based on the antibody-mediated targeting of cytotoxic T-cells. However, the immune system contains another arm, the so-called 'innate' immunity, which could also be employed in immuno-oncology approaches.

Natural Killer (NK) cells, one component of the innate system, possess features that make them attractive as an alternative means of treating cancer. NKs can detect and kill virally infected or transformed cells, through recognition of stress-induced molecules or other changes at the cell surface. NK cells also help mediate antibody-dependent cellular cytotoxicity (ADCC) by destroying cells that have been opsonized by antibodies. Finally, NK cells secrete cytokines and chemokines that expand the immune response.

Among NK cells, a subtype known as 'adaptive' (or memory) has been shown to have enhanced responses against hematologic cancer cells. Adaptive NK cells are most prevalent in people who have been infected with cytomegalovirus (some 50-80 percent of the over-40 population in the United States). When certain receptors (specifically, NKG2C, CD2 and CD16) on these unique cells are bound by single or combinations of individual agonist antibodies, strong anti-tumor responses are generated. Despite these provocative findings, there have been few reported attempts to utilize this potentially very useful subset of cells for cancer therapy.

One means to take advantage of memory NK cells would be to promote their engagement with tumor cells through the use of engineered antibody constructs. NKG2C, an activating receptor that is characteristic of adaptive NKs, could serve to as a 'handle' to co-localize and activate these highly active immune cells, while a tumor-targeting antibody would provide the cancer specificity. Here, we hypothesized that a bi-specific molecule targeting NKG2C and CD22 would show efficacy against hematologic B-cell cancers, which broadly express CD22.

In our studies, we tested various ligands specific to NKG2C, including single-chain human leukocyte antigen E (HLA-E) and commercial NKG2C antibodies, interrogating their ability to specifically bind and activate NKG2C+ cells. We fused these with our lab's well-characterized anti-CD22 antibody and tested these bi-specific constructs for the targeted cytotoxicity of Raji Burkitt's lymphoma cells in standard in vitro killing assays. While still incomplete, the data we have accumulated from these studies will guide future iterations of our NKG2C-specific molecules as we refine our approach for enlisting this uniquely powerful NK subpopulation in cancer immunotherapy.

This work was made possible by a pilot award from the UCDCCC Immuno-oncology Initiative to JT and WM.

4. NORDIHYDROGUAIARETIC ACID-BASED NANOPARTICLES FOR POTENTIATING THE ANTITUMOR IMMUNITY INDUCED BY IDO INHIBITION

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Indoleamine-pyrrole 2,3-dioxygenase (IDO) is an enzyme implicated in the generation of an immunosuppressive tumor microenvironment (TME) through converting antigen-presenting cells from being immunogenic to tolerogenic, producing inhibitory cytokines and activating regulatory T-cells. In cancers, upregulation of IDO has been associated with an increased number of regulatory T-cells. IDO inhibitors can cripple the activities of IDO, thus reduce the population of regulatory T-cells and reverse immunosuppressive TME. However, the clinical studies of IDO inhibitor applications didn't get satisfactory results. Earlier last year, the KEYNOTE-252/ECHO-301 trial of Incyte's IDO1 inhibitor, epacadostat, showed no benefit in progression-free survival (PFS) or overall survival (OS) with combined epacadostat + anti-PD-1 antibody treatment compared to anti-PD-1 monotherapy. This disappointing result led Incyte to shut down the trial. Incyte also cut back their other epacadostat clinical studies, from nine to essentially just two remaining trials of epacadostat in combination with anti-PD-1 in non-small cell lung cancer (NSCLC). We have developed a highly effective and non-toxic nordihydroguaiaretic acid (NDGA) nanoparticles that can not only efficiently deliver NDGA itself and IDO inhibitors but is also able to mechanistically potentiate the antitumor immunity induced by IDO1 inhibition for effective treatment of cancer.

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5. ANALYSIS OF TUMOR INFILTRATING NK AND T CELLS HIGHLIGHTS IL-15 STIMULATION AND TIGIT BLOCKADE AS A COMBINATION IMMUNOTHERAPY STRATEGY FOR SOFT TISSUE SARCOMAS

Sean J. Judge[1], *Morgan A. Darrow*[2], *Steve W. Thorpe*[3], *Alicia A Gingrich*[1], *Edmond F. O'Donnell*[3], *Alyssa R. Bellini*[1], *Ian R. Sturgill*[4], *Logan V. Vick*[4], *Cordelia Dunai*[4], *Kevin M. Stoffel*[4], *Yue Lyu5, Shuai Chen*[6], *May Cho*[7], *Robert B. Rebhun*[8], *Arta M. Monjazeb9, William J. Murphy*[4,7], *Robert J. Canter*[1]
From the Divisions of [1]*Surgical Oncology,* [2]*Pathology and Laboratory Medicine,* [3]*Orthopedics,* [4]*Dermatology, 5Department of Statistics,* [6]*Biostatistics,* [7]*Hematology and Oncology,* [8]*Center for Companion Animal Health, and 9Department of Radiation Oncology, University of California, Davis*

Given the unmet need for novel immunotherapy in soft tissue sarcoma (STS), we sought to characterize the phenotype and function of intra-tumoral natural killer (NK) and T cells to identify novel strategies to augment tumor infiltrating lymphocyte (TIL) function.

Using prospectively collected specimens from dogs and humans with sarcomas, archived specimens, and TCGA data, we evaluated blood and tumor NK and T cell phenotype and function and correlated those with outcome. We then assessed the effects of IL-15 stimulation on both NK and T cell activation and TIGIT upregulation. Finally, we evaluated cytotoxic effects of IL-15 combined with TIGIT blockade using a novel anti-TIGIT antibody.

TILs were strongly associated with survival outcome in both archived tissue and the TCGA, but higher TIL content was also associated with higher TIGIT expression. Compared to blood, intra-tumoral NK and T cells showed significantly higher expression of both activation and exhaustion markers, in particular TIGIT. Ex vivo stimulation of blood and tumor NK and T cells from STS patients with IL-15 further

increased both activation and exhaustion markers, including TIGIT. Dogs with metastatic osteosarcoma receiving inhaled IL-15 also exhibited upregulation of activation markers and TIGIT. Ex vivo, combined IL-15 and TIGIT blockade using STS blood and tumor specimens significantly increased cytotoxicity against STS targets.

Intra-tumoral NK and T cells are prognostic in STS, but their activation is marked by significant upregulation of TIGIT. Our data suggest that combination IL-15 and TIGIT blockade may be a promising clinical strategy in STS.

BLOCK C3 8:00–8:35AM

1. MIR-124-3P SIGNALING IN THE CONTROL OF CANCER CELL ADHESION COMPLEXES AND INVADOPODIA

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Osteosarcoma is a common form of bone malignancy prevalent among children and young adolescent adults, with a great tendency to lung metastasis that causes high mortality rate. Our recent studies using a novel bioengineered miR-124-3p agent has demonstrated the role of miR-124-3p in the inhibition of invasion of osteosarcoma cells as well as lung metastasis in mouse models. This study is to investigate the molecular and cellular mechanisms by which miR-124-3p controls tumor metastasis. LC-MS-based proteomics study identified a set of miR-124-3p-downregulated proteins that could be assembled into multiple biological pathways critical for cancer, such as vesicle-mediated transport, cellular component organization, and cell junction assembly and organization. Among these proteins, we identified and verified plectin (PLEC) as a new direct target for miR-124-3p that links cytoskeleton to cell junctions. Associated with lower levels of PLEC, ITGB1, IQGAP1 and TLN1 proteins, cell adhesion capacity was sharply inhibited by miR-124-3p. Furthermore, the reduction of PLEC by miR-124-3p decreased the ability of cells to form invadopodia, the filamentous actin (F-actin)-based membrane protrusions, and resulted in markable changes of degradation of the extracellular matrix (ECM). Together, our results connect miR-124-3p-PLEC to other known elements in the control of invadopodia, cell adhesion and junctions essential for cancer cell invasion and extravasation towards metastasis.

2. DISTINGUISHING TUMOR MARGINS IN GLIOBLASTOMA MULTIFORME USING FLIM

Silvia Noble Anbunesan[1,2], Alba Alfonso-Garcia[2], Julien Bec[2], Matthew Bobinski[3], Mirna Lechpammer[3], Oluwaseun Adeola Omofoye[3], Orin Bloch[3], Laura Marcu[1,2,3]
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Glioblastoma multiforme (GBM) is a grade IV invasive tumor that is the most devastating type of brain cancer. The best possible treatment for this type of cancer is tumor resection. However, it is difficult to distinguish the tumor from adjacent healthy brain tissues. Histopathological evaluation is the gold standard for identifying positive tumor margins, or the infiltrative edge, but it may take several days to obtain this information. Doctors are faced with the challenge of determining the tumor margins while performing resection mainly based on the images and reports taken prior to the surgery. There is a need for real-time, intraoperative imaging technology that can help provide contrast between tumor and healthy tissue.

Fluorescence lifetime imaging (FLIm) is an optical technology that can help address this challenge. The fluorescence lifetime of brain tissue can be used as an indicator to distinguish between healthy and tumor brain tissue in real-time, thereby guiding the surgeons in the resection process. This study demonstrates the use of a FLIm apparatus that can be clinically used in the operating room to distinguish positive tumor margins in patients diagnosed with GBM, which is typically noted for its infiltrative edges that makes it harder for surgeons to perform clear resection.

Current results show that the FLIm technique reported has the potential to identify tumor infiltrated regions in both the cortical surfaces before resection and in deeper tissues after or during resection in GBM patients. The fluorescence lifetimes and spectral properties observed in tumor infiltrated cortex are significantly different compared to clear cortex regions. Also, tumor margins pathologically marked with increased mitotic activity and vascular proliferation are spectrally different compared with margins that do not exhibit these markers. The current study also identifies the need for and demonstrates the improvement achieved with technical advancements on real-time video feedback. Motion correction was applied to the FLIm maps for accurately tracking the movements of the surgical field of view as captured by the surgical microscope. This provides an enhanced visual experience for the neurosuergeons. The results demonstrate that the FLIm technique discussed can be used to study the metabolic activity of brain tissue in vivo in real time that can help guide the neurosurgeon in performing tumor resection during craniotomy procedures.

This study was supported by the National Institutes of Health (R21CA178578), the University of California, Davis Comprehensive Cancer Center's Brain Malignancies Innovation Group, and Carl Zeiss. The author wishes to thank Marcu Lab members for their contribution towards data acquisition and visualization.

3. DESIGNER EDIBLE CROPS TO DELIVER ANTI-CANCER COMPOUNDS

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Small molecules found in cruciferous vegetables (e.g., broccoli) have been established as precursors of chemopreventive agents by the NCI. However, effective release of these agents often require enzyme to convert them from an inactive to active form. One such molecule, glucoraphanin, requires a myrosinase to activate it to its chemopreventive product, sulforaphane. While the benefits of a high sulforaphane diet are becoming increasingly well understood, intake of sulforaphane through foods like broccoli is still far below the amounts recommended by the National Cancer Institute. Thus, increasing access to such compounds in widely consumed vegetables provides a transformative means to abate cancer through diet, nutrition, and the agricultural crops that we grow. Agriculture, food, and nutrition all play a key role in our health and the prevention of cancer. We have focused on developing strategies to enhance the bioavailability of target phytochemicals in order to increase intake of a target plant-derived compound linked to chemoprevention.

4. ULTRALOW-DOSE CT IMAGING WITH DEEP LEARNING NOISE REDUCTION ON THE EXPLORER TOTAL-BODY PET/CT SCANNER

Jesse Ahlquist[1], Yasser G. Abdelhafez[2], Lorenzo Nardo[2], Ramsey D. Badawi[1,2], Jinyi Qi[1], Guobao Wang[2]
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Introduction: The EXPLORER PET-CT scanner offers ultrahigh sensitivity for fast and low-dose PET scans and the ability of covering the entire body simultaneously for dynamic PET imaging. It has been routinely used for both clinical scans and research studies. In many situations such imaging of healthy subjects, longitudinal tracking of subjects with chronic diseases and imaging of pediatric patients, ultralow-dose CT imaging is desirable in order to minimize the radiation exposure from a combined PET/ CT scan. While an ultralow-dose CT scan can be sufficient for PET attenuation correction, it may compromise the CT image quality for anatomic localization and potentially quantification such as in the liver for steatosis evaluation. The objective of this paper is to demonstrate the potential of deep learning noise reduction for ultralow-dose CT imaging on the EXPLORER with an evaluation emphasis on liver CT quantification using clinical patient scans.

Methods: Thirty patients who underwent a dual-time-point PET/CT scan were retrospectively included in this study. Each patient received the first PET/CT scan at 60 minutes post FDG injection and the second PET/CT

scan at 90 minutes. The first attenuation correction (AC) CT scans were all performed with regular low-dose (RLD) technique factors (140 kVp, 50 mAs; effective dose estimate: 10 mSv). The second AC-CT scans were performed using ultralow-dose (ULD) technique factors (140 kVp, 5 mAs; effective dose estimate: 1 mSv). The patient datasets were further divided into separate analysis groups based on their scan position (arms-up: 24 subjects vs. arms-down: 6 subjects). The deep learning (DL) denoising model was trained using the Residual Encoder-Decoder Convolutional Neural Network (RED-CNN) model based on the AAPM Mayo CT datasets. The ULD images and their deep learning denoised version (ULD-DL) were compared with the corresponding RLD CT scan of the same patient as the reference. Quantitative comparison was conducted for CT liver quantification (in Hounsfield units) using spherical liver ROI's (50 mm in diameter) across the three approaches (ULD, ULD-DL, RLD).

Results: The deep learning denoising was successfully applied in all patient scans. Compared with the regular low-dose scan, the ULD scan induced high noise across the majority of body sections. In addition, streak artifacts appeared around the shoulder and neck in the arms-up group and in the liver in the arms-down group. The ULD-DL approach dramatically reduced both noise and artifacts as compared to ULD. The ULD-DL approach reduced the noise standard deviation of the liver ROIs by a factor of 5 as compared to the ULD approach. ROI quantification by ULD and ULD-DL was highly correlated with the regular low-dose scans. The correlation was much higher in the arms-up group than in the arms-down group.

Conclusion: Deep learning noise reduction is promising to improve ultralow-dose CT scans on the EXPLORER. Our study indicated that the ultralow-dose protocol provides comparable performance to regular low-dose protocol for CT liver quantification. Our results also indicate that compared with the arms-up group, the arms-down scanning position may result in severe artifacts which compromise liver CT quantification in both regular low-dose and ultralow-dose scans. Furthermore, deep learning can significantly reduce image noise without compromising liver CT quantification in the arms-up group. However, in the arms-down group, while deep learning can greatly reduce artifacts, improvement in liver quantification may still be limited.

BLOCK C4 8:00–8:35AM

1. THERAPEUTIC TARGETING OF ROR-Γ INDUCES GENOME-WIDE REPROGRAMMING OF CHROMATIN LANDSCAPES IN PROSTATE CANCER

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Our previous study found that retinoid acid receptor-related orphan receptor γ (ROR-γ) 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 poorly understood. Using ChIP-seq and ATAC-seq, we demonstrated here that treatment of CRPC cells with ROR-γ antagonists not only strongly suppressed genome-wide histone acetylation and H3K4 methylation but also markedly decreased the chromatin accessibility at enhancer and promoter regions. Interestingly, we found that the diminished chromatin accessibilities were largely overlapped with AR binding and gene activation linked H3K27ac epigenetic marks. Our further analysis revealed that the ROR-γ antagonist not only diminished chromatin accessibility it also potently induced "open" chromatin structures at gene regulatory regions, highlighting its remarkable activity in reprogramming chromatin structures. Importantly, we found that genes with altered chromatin accessibility are also associated with Wnt signaling and regulatory networks of stem cell pluripotency. Overall, our work provides new insights of ROR-γ function in chromatin landscape reprogramming as well as the mechanism of action of therapeutics targeting ROR-γ in advanced prostate cancer.

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2. MICROBIAL METABOLITE MIMICRY, A NANO-DRUG FOR COLON CANCER TREATMENT

Ying Hu[1], *Ruiwu Liu*[2], *Kit S. Lam*[2], *Yu-Jui Yvonne Wan*[1]
[1]*Department of Medical Pathology and Laboratory Medicine,* [2]*Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis*

A standard chemotherapy regimen for colorectal cancer (CRC) contains a complicated mixture of drugs that must be injected, causes multiple side effects, and leads to drug resistance. Development of an oral, low-toxicity treatment would greatly improve care for CRC patients. Our strategy is to target gut dysbiosis (gut microbiome imbalance) via the pathway by which CRC arises in the first place.

To understand colon carcinogenesis, we profiled transcriptomes in normal colons and CRC specimens. Compared with normal colons, human CRC specimens have elevated protein deacetylases and reduced bacterial metabolites, i.e., short-chain fatty acids (SCFAs) harboring histone deacetylase (HDAC) inhibitory properties. In the gut, HDAC inhibitors can induce the expression of intestinal ALDH1A, which generates retinoic acid (RA) in dendritic cells. Accordingly, our data showed that RA signaling is reduced in human CRC specimens. Furthermore, we studied whether supplementation of RA and HDAC inhibitors, including butyrate or suberanilohydroxamic acid, can treat colon cancer. The data showed a combination of RA and HDAC inhibitor is more effective than single chemicals in inducing apoptosis of colon cancer cells. Moreover, the combination treatment can reduce colon cancer growth in xenograft mouse models. The mechanism of action is in part due to tumor suppressor miR-22 induction, which silences the abundant protein deacetylases present in human CRC. Silencing the protein deacetylases HDAC1 and HDAC4 leads to the induction and nuclear export of NUR77 and RARβ to target mitochondria, resulting in apoptosis of cancer cells.

We therefore have produced nano-drugs combined RA and HDAC inhibitor. RA-. One of these nanodrugs, named BURA, was synthesized by covalently linking butyric acid (BU) and all-trans RA to polyvinyl alcohol (PVA), assembling into nanomicelles. BURA50 and BURA100 were produced with a molar ratio of BU:RA = 50:1 or 100:1, respectively. This strategy has several advantages: (1) the nano-drug can be delivered orally to target the gut microbiota; (2) BU and RA can be released simultaneously to exert their combined benefits, which does not occur when only one chemical is used; and (3) the molar ratio of BU and RA can be adjusted to reduce the unwanted side effects of RA. Excitingly, both BURA50 and BURA100 revealed promising results in treating colon cancer in orthotopic colon cancer induced by azoxymethane and dextran sodium sulfate in mice.

Furthermore, BURAs did not have any apparent toxicity in healthy mice and colon cancer-bearing mice. In summary, BURA50 and BURA100 are orally delivered to target microbiota-regulated signaling, which is novel for CRC treatment.

3. BLADDER CANCER METABOLOMICS IDENTIFIES IMPORTANT DIFFERENCES IN LIPID METABOLITES BETWEEN METASTATIC AND NON-METASTATIC TUMORS

M. Malvina Tsamouri, DVM, Shamira Sridharan, PhD, Blythe P. Durbin-Johnson, PhD, Marc A. Dall'Era, MD, Paramita M. Ghosh, PhD

Introduction: For muscle invasive bladder cancer (MIBC), the standard treatment is radical cystectomy (RC) with or without neoadjuvant chemotherapy (NAC) or trimodal therapy with maximal resection and combination chemo-radiation. Local recurrence rate ranges between 30 and 54% while distant recurrence is often reported in up to 50% of cases. For metastatic bladder cancer, standard treatment options include cisplatin- or carboplatin-based chemotherapy, immunotherapy with PD-1 and PD-L1 inhibitors and targeted therapy using erdafitinib for patients with FGFR3 and FGFR2 mutations. Many of these treatments can be used as adjuvant or neoadjuvant therapy for patients at high risk of early recurrence; however, currently there is no systematic mechanism to detect patients at risk for early recurrence. Therefore, the overall goal of the current proposal is to identify patients who are likely to experience early recurrence despite RC either with or without NAC.

Methods: We characterized the global metabolome of 33 high-grade bladder cancers from radical cystectomy specimens. Of all 33 patients, 13 (39.4%) would later develop metastases within the next 2 years, while 18 (54.5%) did not (status of 2 patients are unknown). We used targeted and untargeted metabolomic approaches

with gas chromatography- time-of-flight mass spectrometry (GC-TOF MS) to profile primary metabolites, hydrophilic interaction liquid chromatography MS (HILIC-QTOF MS) to profile biogenic amines and liquid chromatography charged surface hybrid MS (LC-CSH-QTOF MS) to characterize complex lipids. The primary outcome was differences in metabolite levels stratified by metastatic disease status. Metabolite levels were also correlated with clinical variables including age, body mass index, smoking status and receipt of neoadjuvant chemotherapy. Differences were significant when log2FoldChange >1.5 fold and $p<0.05$

Results: 1225 known metabolites of a total of over 4600 were characterized in the manner described. LPC(22:5) was increased, while other metabolites including N-ε-acetyl lysine (NEAL), 1-hexadecylamine (HDA) and N-Dimethyldodecylamine N-oxide (DMDAO) were decreased. Next, patients were classified as those who received NAC (n=11) or did not (n=21), and the ability of the compounds to predict later mets was investigated. Significantly, N-ε-acetyllysine (NEAL) was effective in differentiating patients who would develop later mets if they did not have prior NAC, while 1-hexadecylamine (HDA) was able to differentiate patients who would develop later mets only if they had prior NAC. The area under the ROC curve (AUC) changes accordingly, with NEAL showing improved selectivity and specificity in patients who do not undergo NAC, while failing to show any predictive effect in patients who do undergo NAC. On the other hand, HDA was highly differentiated and predictive of later metastases in patients who underwent NAC, while having no effect whatsoever in patients who did not undergo NAC.

Conclusions: There is an unmet need for the development of a panel of biomarkers that can identify MIBC patients at high risk for recurrence and metastasis following RC. The development of such a panel is of utmost necessity, so that such patients, who do not yet indicate the existence of micro- or gross metastases, be aggressively treated with adjuvant chemo-, immune- or targeted therapy following RC to prevent or delay the onset of loco-regional or distant metastases.

4. MISMATCH REPAIR PROTEINS REGULATE HOMOLOGOUS RECOMBINATION TO PREVENT GENOME REARRANGEMENTS

Diedre Reitz[1], *John McPherson*[2], *Wolf-Dietrich Heyer*[1,3]
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Homologous recombination (HR) is the primary high-fidelity mechanism of DNA repair in the cell. Its faithfulness comes from the fact that the reaction proceeds through a series of reversible recombination intermediates, each of which is subject to extensive regulation. Two critical regulators of the HR pathway are the mismatch detecting heterodimers, Msh2-Msh3 and Msh2-Msh6. In vivo studies indicate that Msh2-Msh3 and Msh2-Msh6 act as a barrier to prevent recombination between mismatched, or “homeologous”, regions.

This is significant, because homeologous recombination has the potential to lead to mutagenesis and genome rearrangements. While the Msh2 complexes likely act by recruiting effectors to reverse key recombination intermediates, this has not yet been formally demonstrated, because until recently it has been impossible to directly quantify these intermediates. Moreover, though MSH2, MSH3, and MSH6 are frequently mutated in certain cancers, whether tumors deficient in these proteins display the genome rearrangements that would be predicted from loss of regulation of HR is unknown due to limitations in current sequencing technologies.

Our project aims to address these gaps in the published literature by using genetic and biochemical methodologies in model organism S. cerevisiae in combination with cutting-edge single-molecule long-read sequencing analysis of patient tumor samples. To map the factors responsible for preventing homeologous recombination in vivo in budding yeast, I will adapt two proximity-ligation based assays recently developed by the Heyer laboratory (1-3) to detect recombination intermediates formed between the site of a DNA double-stranded break and matched or mismatched donors. I will then reconstitute this mechanism using purified budding yeast and human proteins, and perform experiments to understand how Msh2-Msh3 and Msh2-Msh6 interact with their effectors. These studies will at last provide insight into the precise mechanism through which Msh2-Msh3 and Msh2-Msh6 suppress homeologous recombination. Finally, we will use long-read sequencing to sequence matched tumor and blood samples from patients with MSH2, MSH3, and MSH6 deficient tumors.

Long-read sequencing has the ability to identify genome rearrangements caused by promiscuous recombination between mismatched, repetitive elements, whereas paired-end short-read sequencing cannot identify repeat recombination between repeats longer than the length of the sequenced fragment. Importantly, our sequencing analysis of patient tumor samples will demonstrate the clinical significance of loss of regulation of the HR pathway in MSH2, MSH3, and MSH6 deficient tumors. We anticipate that eventually our work will allow for improved diagnostic testing and targeted therapies to treat these tumors.

This project was recently initiated, and I will present the concept and preliminary results.

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5. BIOENGINEERED MICRORNAS IN THE CONTROL OF FOLATE CYCLE RELATED ONE-CARBON METABOLISM IN NSCLC METABOLISM

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Lung cancer remains as the leading cause of cancer deaths worldwide and in the US, of which non-small cell lung cancer (NSCLC) accounts for 80-85%. Very recently, we have established a novel technology to achieve in vivo fermentation production of bioengineered miRNA agents for the study of cancer biology and new therapies. Using recombinant miRNA molecules produced and folded in living cells, we identified a number of the top most effective miRNAs against non-small cell lung cancer (NSCLC) cell variability, among which miR-22-3p, miR-9-5p and miR-218-5p are all predicted to interfere with folate cycle of one-carbon metabolism. The serine hydroxymethyltransferase-1 (SHMT-1), a tumor biomarker and important enzyme in folate biotransformation, was verified as a new target for both miR-9-5p and miR-218-5p. The methylenetetrahydrofolate dehydrogenase 1 like (MTHFD1L) and methylenetetrahydrofolate dehydrogenase-2 (MTHFD2) were proven to be regulated by miR-9-5p directly. Furthermore, both methylenetetrahydrofolate reductase (MTHFR) and MTHFD2 were significantly suppressed by miR-22-3p in NSCLC cells. Selective LC-MS/MS methods revealed that folate metabolites and amino acid metabolome were altered remarkably by individual miRNAs in human NSCLC cells. Further isotope labeled glucose feeding experiments showed that miR-22-3p affected intracellular supply of serine through the inhibition of glucose transporter GLUT1, and miR-9-5p and miR-218-5p decreased serine levels via downregulation of serine biosynthesis enzymes.

Consequently, glycolytic rate and mitochondrial function were significantly inhibited in NSCLC cells by these miRNAs, accompanied by cell cycle arrest, ROS accumulation and NADP+/NADPH imbalance. Finally, miR-22-3p-loaded lipopolyplex was shown to significantly inhibit tumor growth in NSCLC patient-derived xenograft (PDX) mouse models in vivo, attributable to on-target actions. In conclusion, our results demonstrate that bioengineered miR-22-3p, miR-9-5p, and miR-218-5p act on folate cycle to suppress NSCLC cell metabolism, among which miR-22-3p is effective to control NSCLC tumor growth in PDX mice. These findings provide new insights into mechanistic actions of tumor suppressive miRNAs and development of new therapeutic strategies.
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BLOCK D1 8:40 – 9:15AM

1. TOTAL-BODY DYNAMIC PETOF METASTATIC CANCER: FIRST PATIENT RESULTS

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Objectives: Dynamic 18F-FDG PET with tracer kinetic modeling has the potential to better detect lesions and assess cancer response to therapy. This potential, however, has not been fully studied in the clinic because conventional PET scanners have a limited axial field-of-view (15-30 cm) and are not capable of simultaneous dynamic imaging of widely separated lesions. The EXPLORER, a total-body (194 cm axial field-of-view) high-sensitivity PET/CT scanner, is being used for routine studies. To test its capability for kinetic modeling and parametric imaging of cancer, we designed a clinical study on total-body dynamic PET in patients with metastatic cancer. The objective of this paper is to report the results from the first patient scan and to demonstrate total-body dynamic PET for improved tumor detection and for enabling multiparametric characterization of metastases.

Methods: One patient with metastatic renal cell carcinoma was scanned on the uEXPLORER total-body PET/CT scanner. Prior Ethics Committee/IRB approval and informed consent were obtained. The subject was injected with 10 mCi of 18F-FDG. Total-body dynamic data were acquired in list-mode format for 60 minutes and binned into 29 time frames (6x10s, 2x30s, 6x60s, 5x120s, 4x180s, 6x300s). The static PET standardized uptake value (SUV) was calculated for the last time frame (55-60 minute). Kinetic modeling using the standard irreversible two-tissue compartmental model was performed for regional quantification in sixteen regions of interest (ROI) including major organs and multiple metastases. The time activity curve (TAC) from the left ventricle was used as the image-derived input function. The fractional blood volume (vb) and time delay were also included and jointly estimated in the kinetic model for joint estimation. The FDG net influx rate Ki was then calculated from the estimated micro kinetic parameters. Kinetic modeling was further implemented voxel-by-voxel to generate parametric images of the kinetic parameters. The kinetic data were then used to explore two aspects of total-body parametric PET of cancer: tumor detection and tumor characterization.

Results: The dynamic FDG-PET scan of the first patient was successful and provided dynamic imaging and visualization of the spatiotemporal pattern of multiple distant metastases. Six metastases were identified. The comparison between Ki and SUV for tumor-to-liver ratio indicated that Ki improved tumor contrast by a factor of about 3 as compared to SUV. For renal lesion detection, the Ki image effectively suppressed the background activity and significantly enhanced the lesion contrast, while the SUV image quality was compromised by the physiological excretion of FDG in renal pelvis. The parametric images of Ki and two FDG perfusion/transport parameters - fractional blood volume vb and blood-to-tissue delivery rate K1 – showed different spatial patterns across organs. The three parameters reflect different physiological aspects and can provide a multiparametric characterization of the metastases for improved subtyping. While the Ki values of different tumors were in a similar range, their K1 and vb values spread more widely, which may be related to the potential heterogeneity of local blood supply and tumor microenvironment.

Conclusion: We successfully conducted the first total-body dynamic FDG-PET scan of a patient with metastatic cancer on the uEXPLORER. It is feasible to perform total-body kinetic modeling and parametric imaging of metastatic cancer using this device. Parametric image of Ki improved tumor contrast over SUV in general and specifically led to improved lesion detection in renal cortex which has been historically challenging. Total-body kinetic quantification also provides multiparametric characterization of tumor metastases and organs of interest (e.g., spleen and bone marrow), which can be used for more quantitative assessment of tumor response and normal tissue effects following a range of anticancer therapies.

Acknowledgements: This work is supported in part by NIH grant K12 CA138464, R01 CA206187 and a UCD CCC CIP Pilot Grant.

2. CROSS-RESISTANCE AMONG NEXT GENERATION ANTI-ANDROGEN DRUGS THROUGH THE AKR1C3/AR-V7 AXIS IN ADVANCED PROSTATE CANCER

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Introduction and Objectives: The next generation anti-androgen drugs, XTANDI® (Enzalutamide), ZYTIGA® (Abiraterone acetate), ERLEADA™ (Apalutamide) and NUBEQA (Darolutamide) extend survival times and improve quality of life in advanced prostate cancer patients. Despite these advances, resistance occurs frequently and there is currently no definitive cure for Castration-Resistant Prostate Cancer (CRPC). Our previous studies identified that similar mechanisms of resistance to enzalutamide or abiraterone occur following treatment and cross-resistance exists between these therapies in advanced prostate cancer. In this study, we will investigate the role of the AKR1C3/AR-V7 axis in apalutamide and darolutamide resistance.

Methods: C4-2B cells were chronically exposed to increasing concentrations of apalutamide (5 μM ~ 40 μM) by passage in media containing apalutamide for >12 months in complete FBS and stored for further analysis. Cells resistant to apalutamide were referred to as C4-2B APALR. The effects of AKR1C3 expression and activation were examined by knock down of AKR1C3 expression using lenti-shRNA or inhibition of AKR1C3 enzymatic activity by indomethacin. AR and AR-V7 activity were determined by luciferase reporter assay. The effects of AKR1C3 activation on anti-androgen sensitivity were examined by growth assay and clonogenic assay.

Results: Enzalutamide and abiraterone resistant prostate cancer cells are further cross-resistant to apalutamide and darolutamide. Mechanistically, we have determined that the AKR1C3/AR-V7 axis confers this cross-resistance. Knockdown of AR-V7 in enzalutamide resistant cells re-sensitize cells to apalutamide and darolutamide treatment. Furthermore, targeting AKR1C3 re-sensitizes resistant cells to apalutamide and darolutamide treatment through AR-V7 inhibition. Chronic apalutamide treatment in C4-2B cells activates the steroid hormone biosynthesis pathway and increases AKR1C3 expression which confers resistance to enzalutamide, abiraterone and darolutamide.

Conclusion: Apalutamide and darolutamide share similar resistant mechanisms with enzalutamide and abiraterone. The AKR1C3/AR-V7 complex confers cross-resistance to second generation AR-targeted therapies in advanced prostate cancer.

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3. THE ROLE OF AXL TYROSINE KINASE IN THE TUMOR-IMMUNE MICROENVIRONMENT OF MELANOMA

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Introduction: The TYRO3, AXL and MERTK (TAM) receptor tyrosine kinase (RTK) family have been associated with a number of human cancers, including melanoma. Effects attributed to oncogenesis and metastasis (epithelial-to-mesenchymal transition) of the TAM receptors have been described. Recent evidence suggests Axl may play a significant role in inflammation but its role in tumor evasion of immune surveillance and response to immunotherapy has not been well defined. Therefore, we aim to examine the role of Axl expression and function in melanoma with multiple methods of ligand, Gas 6, inhibition. Specifically, we aim to elucidate the mechanisms by which AXL TK mediates tumor associated macrophage phenotype and resistance to modern therapies in both clinical and preclinical models of melanoma.

Methods: TCGA-SKCM melanoma tumor mRNA expression and clinical data for metastatic melanoma patients were downloaded from the GDC legacy archive (https://portal.gdc.cancer.gov/legacy-archive) (n =

471). Biomarkers were defined as “high” or “low” expression in each patient. Differences in Kaplan-Meier survival curves based on level of expression were tested using G-rho family tests. Strength of relationships between biomarkers were measured using Pearson’s correlation. All statistical analysis were performed using R package “survival”. Blood obtained from melanoma patients banked through the UC Davis biorepository was evaluated for serum levels of sAXL by ELISA. In vitro assays were conducted to examine the effect of AXL inhibition on melanoma tumor cell expression and function and evaluated by

Results: Stage IV patients responding to Pembrolizumab demonstrated significantly lower AXL levels compared to non-responders (p<0.0.5). Serum detectable sAXL significantly increased by stage with highest levels noted in stage IV patients (p=0.03). Association between AXL expression, inflammatory biomarker signatures, and survival outcomes varied significantly between normal weight, overweight, and obese patients as well as by gender. In the normal weight population, high CD8 (p=0.0093), PD1 (p=0.0093) and CD84 (p=0.022) were associated with improved survival. In the overweight population, high CD8 (p=0.0098), PD1 (p=0.0004) and CD84 (p=0.0081) were associated with improved survival, while high Gas6 (p=0.029) and MERTK (p=0.043) were associated with decreased survival. And in the obese population, high AXL expression was associated with improved survival (p=0.004), while CD8 (p=0.91) and PD1 (p=0.89) demonstrated no association. In correlation analysis, AXL expression was most closely associated with macrophage markers CD163 (r=0.52), CD84(r=0.56) and MS4A4A(r=0.53) in the obese but not the normal weight population. Melanoma cell migration was significantly increased with exogenous Gas6 exposure and this effect was inhibited by warfarin (P<0.05)

Conclusions: Taken together, these data suggest that melanoma cell behavior and immunologic response in melanoma patients is associated with AXL activity. AXL appears to mediate response in the obese population by a macrophage-driven mechanism as opposed to T cell mediation. Further definition of the potential therapeutic impact of AXL directed targeting in melanoma is warranted.

4. BIOMARKER ANALYSIS OF NEOADJUVANT INTRALESIONAL THERAPY IN HIGH RISK MELANOMA

S.Gholami S. Chen, R. Nielsen, R. Bold, R. Canter, E.M. Maverakis, A.R. Kirane

Introduction: Despite the recent notable advances in the treatment of advanced melanoma with application of growing immunotherapies, patterns of response and factors resulting in treatment failure are poorly understood. The application of these therapeutics has been limited in the neoadjuvant setting, particularly in earlier stage disease, even though this strategy has improved tolerance and efficacy with other modalities of therapy in most solid cancer types. Survival remains significantly poorer for thick and ulcerated lesions (T3b/T4) with less than 50% survival at 5 years independent of other prognostic indicators. Oncolytic viral therapies (OVT) stimulate or suppress the immune system in different ways to stop cancer cells from growing and intra-lesional OVT has demonstrated comparable efficacy and durability with greater tolerability than most effective systemic therapy. Talimogene laherparpvec (T-VEC) is the only phase III approved intra-lesional therapy in melanoma and has demonstrated significant overall response rate (64%) and bystander effect (34% in uninjected lesions) in the therapeutic setting for advanced disease.

Methods: We propose an open-label, Phase 2 study of Talimogene laherparpvec (T-VEC), in the neoadjuvant setting for patients with high-risk, resectable primary cutaneous melanoma prior to definitive excision. This strategy has not yet been explored in early phase disease despite positive results in advanced melanoma. The central hypothesis of this proposal is that neoadjuvant intralesional therapy with T-VEC in high risk melanoma will effectively treat local and subclinical distant disease by enhanced immune recognition, immunomodulation of the nodal basin, and still allow for standard of care surgery. The primary aim of this study will be to evaluate for histologic response of melanoma with secondary aim to determine changes in immune response and draining sentinel nodes as well as relationship of immune phenotype to response rate and nodal burden. We plan for thorough exploratory analysis of genetic and microenvironmental changes to identify actionable targets in incomplete response as well changes in sentinel burden and subsequent rates of locoregional disease control and recurrence-free survival in long term follow up. We predict that histologic clearance of the primary tumor in the surgical specimen will be associated with improved RFS. 62 patients will be enrolled over the course of 2 years.

Conclusions: Our ability to predict non-responder from responder to immunotherapeutic agents such as T-VEC is not yet defined and the risk of universal exposure to systemic agents may outweigh the hypothesized benefit. Importantly, mechanistic dissection of pathways and immunological signatures of response offer the promise of a more rational and targeted selection of immunotherapy. This study would be first in kind to target earlier stage melanoma in the neoadjuvant setting with a less toxic intra-tumoral immunotherapy with key correlative endpoints regarding mechanism of response.

BLOCK D2 8:40 – 9:15AM

1. BI- AND TRI-SPECIFIC ANTIBODIES FOR HEMATOLOGIC MALIGNANCIES AND SOLID TUMORS

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Harnessing the power of the immune system to fight cancer has resulted in a cancer therapy revolution. Two landmark advances are bispecific antibodies and immune checkpoint blockade. Bispecific antibodies simultaneously bind target tumor cells and T cells, resulting in MHC-independent T cell activation and target cell killing. Blinatumomab, the first successful dual-specificity recombinant antibody in cancer therapy, is a bispecific T cell engager (BiTE) that binds CD19 in malignant B cells and CD3 in T cells. It has shown remarkable success in B-cell malignancies. However, it is becoming evident that relapses may be due to CD19 antigen loss. Immune checkpoint blockade therapy relies on blocking T cell inhibitory signals triggered by the tumor or its microenvironment. Currently approved checkpoint inhibitors are antibodies that block PD-1 or CTLA-4 signaling. Immune checkpoint blockade has resulted in unprecedented responses in some solid tumors, but not all patients respond, and toxic side effects are severe in a significant number of patients. This toxicity arises from systemic activation of the immune system.

CD22 is broadly expressed in B cell malignancies and has been validated as a therapeutic target in the form of monoclonal antibodies, antibody-drug conjugates and CAR-T cells. We hypothesized that a BiTE targeting CD22 could represent a therapeutic alternative to blinatumomab in non-Hodgkin's lymphoma (NHL) and B cell acute lymphoblastic leukemia (ALL) patients, particularly those with antigen loss driven relapses. Preliminary data suggests that CD22 is also expressed in some non-hematologic malignancies. Accordingly, we propose the hypothesis that CD22-targeted immunotherapy is effective against CD22+ solid tumors, and that a tri-specific antibody targeting CD22, CD3 and PD-1 will engage T cells to kill tumor cells while localizing checkpoint blockade to the tumor microenvironment (as opposed to systemic), making it more efficacious and less toxic.

To test these hypotheses, we used standard molecular biology techniques to construct expression plasmids from publicly available IgG sequences of the desired specificities. We engineered these sequences as tandem single chain variable fragments (scFv) and as binding modules with swappable specificity. We expressed recombinant proteins in Expi293F cells. We tested in vitro killing by incubating target cells (leukemia, lymphoma and sarcoma cell lines) with immune effector cells from healthy donors (PBMCs or untouched purified T cells) in the presence of the biologics under analysis. In vivo efficacy was tested in NSG mice grafted with human leukemia cells and normal human PBMCs.

We successfully produced αCD22-αCD3 BiTEs in a variety of formats and confirmed their in vitro activity against 3 NHL, 2 ALL and 3 sarcoma cell lines. Killing activity correlated with E:T ratios and dose. In NHL and ALL, potency was comparable to the positive control blinatumomab. As expected, killing activity correlated with T cell expansion (by absolute counts of CD3+ cells), activation (by CD69, CD25 and IFNγ) and a memory phenotype. In vivo, treatment with αCD22 BiTE resulted in increased survival vs untreated controls (53 vs 37 days). In solid tumors, our αCD22 BiTE showed lower in vitro activity against sarcoma cells when compared to B cells used as targets. This may be explained by the fact that CD22 density on the cell surface is over 1,000-fold lower in the solid tumor cell lines we tested. Regardless, up to 50% killing of sarcoma cells was observed with αCD22 BiTE using PBMCs as effector cells. These results need to be confirmed in vivo using PDX models. If successful, our αCD22 BiTE could represent a breakthrough in the treatment of sarcoma, and

possibly other solid tumors. Lastly, we developed a tri-specific biologic targeting CD22, CD3 and PD-1. While there are currently no robust in vitro PD-1 block assays, our preliminary results using long-term tumor outgrowth assays show increased activity of the tri-specific vs the bi-specific alone. Confirmation of T cell engagement and local PD-1 blockade will need in vivo experiments in immunocompetent animals.

This work was made possible by a pilot award from the UCDCCC Immuno-oncology Initiative to GB and WM. In summary, we have developed bi-specific T cell engagers targeting CD22 and validated their therapeutic potential against CD22+ malignancies in vitro and in vivo. The CD22 BiTE is effective at inducing T cell activation only in the presence of target cells, and it could represent a valid therapeutic alternative to blinatumomab. We have also developed a promising tri-specific antibody that may achieve T cell activation and simultaneous PD-1 blocking at the tumor site, potentially triggering tumor cell killing and inhibiting checkpoint blockade with no, or lower, systemic toxicity.

2. PRO-TUMORIGENIC EFFECTS OF OLFACTOMEDIN-LIKE 3 IN GLIOMA

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Despite the completion of greater than 450 NIH-sponsored clinical trials, glioblastoma multiforme (GBM) remains a uniformly lethal brain tumor. Under the influence of glioma-derived transforming growth factor-beta (TGF- β), glioma-associated microglia (GAM) display negligible anti-tumor function and are polarized to produce molecules that promote glioma growth and invasion. Although TGF- β has a significant role in GBM progression, failed clinical trials suggest a complex role in GBM pathogenesis similar to non-CNS cancer. Thus, an improved understanding of the TGF- β /GAM axis is critical to refine our therapeutic approach toward precise molecular targets. OLFML3, which encodes the secreted glycoprotein olfactomedin-like 3 (OLFML3), is increased 9-fold in human glioma tissue. Although poorly studied within the context of GBM, OLFML3 contributes to non-CNS tumor progression through promotion of angiogenesis and neoplastic cell growth kinetics. Therefore, we hypothesized that TGF-β-induced, microglial-derived OLFML3 polarizes microglia cells toward a pro-tumorigenic phenotype, supports angiogenesis and promotes the malignant phenotype of glioma cells. We first demonstrated that Olfml3 is a direct target gene of all three TGF- β isoforms in microglia, but not primary brain endothelial cells nor a mouse glioma cell line (GL261). Further, our data suggests that Olfml3 is required for several of the TGF- β -induced pro-tumorigenic effects of GAM. Leveraging an Olfml3 knockout cell line generated in our laboratory, we demonstrated that loss of Olfml3 increased mRNA levels of pro-inflammatory mediators Tnf and Nos2 as well as H2-Ab1, which encodes MHC II, following exposure to TGF-β. Moreover, production of platelet derived growth factor alpha, a key pro-tumoral growth factor, was attenuated. Importantly, the effects of OLFML3 were non-cell autonomous. Exposure to recombinant human OLFML3 (rhOLFML3) generated in our laboratory increased all phases of angiogenesis in primary mouse brain endothelial cells (ECs), as measured by cellular proliferation, migration, and tube formation. Moreover, a linear increase in migration of GL261 cells was observed following exposure to increasing concentrations of rOLFML3. However, only a single concentration of rOLFML3 increased GL261 invasion, suggesting a concentration-dependent cellular response. Taken together, our data suggest a supportive role for microglia-derived OLFML3 in glioma progression through functioning as a gatekeeper for TGF- β -induced microglial gene expression and promotion of angiogenesis and glioma cellular migration.

3. IMPACT OF THE ARYL HYDROCARBON RECEPTOR SIGNALING PATHWAY IN BREAST CANCER DEVELOPMENT

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Activation of the aryl hydrocarbon receptor (AhR) through environmental exposure to toxicants including dioxins and many other pollutants in the environment, which can activate the AhR can lead to severe adverse health effects and promotion of cancer development. In the current study we examine the mechanisms to inhibit the development breast cancer by suppressing the AhR activity and using the Repressor protein of the AhR (AhRR). While AhRR may block the canonical AhR pathway, the function of AhRR in the development of breast cancer is not well known. Results of a syngeneic murine mammary tumor model of mammary tumor cells (E0771) xenografted into B6 wt and transgenic mice (AhRR Tg mice) that overexpresses AhRR indicate that AhRR is able to suppresses AhR-driven and inflammation-induced mammary tumors in mice.

Furthermore, we used the polyoma middle T antigen (PyMT) model of ER-negative metastatic breast cancer and found that the expression of AhR increases in mammary tissue during tumor progression in PyMT mice and expression of AhR gene targets and inflammatory markers (e.g. COX-2 and C/EBPβ) increased accordingly. In contrast, the expression of the tumor suppressor gene AhRR decreased in mammary tumors of PyMT mice which mimics AhR and AhRR expression patterns described in human breast cancer. AhRR overexpression in mammary epithelial cells (MEC) isolated from mammary tissue of PyMT mice enhanced apoptosis induced by chemotherapeutics (doxorubicin and laptinib) and reduced sensitivity to AhR- and LPS-induced inflammatory markers. Further we generated PyMT/AhRR+ mice and found that AhRR overexpression significantly delayed onset of palpable tumors and the number of lesions detected at necropsy compared to PyMT/wt mice. Thus, AhRR expression increases tumor latency and decreased tumor incidence.