UC DAVIS HEALTH | COMPREHENSIVE CANCER CENTER

28th Annual Cancer Research Symposium
October 6 and 7, 2022

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

FROM THE DIRECTOR

I am pleased to welcome you to the UC Davis Comprehensive Cancer Center's 28th Annual Symposium. In its 28th 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 in-person event will be organized into four main sessions and two poster sessions: Thursday, Session I – Population Sciences and Health Disparities, chaired by Dr. Shehnaz Hussain; Session II – Diverse Career Development and Education, chaired by Dr. Frederick Meyers and Dr. Luis Carvajal-Carmona; Session III – Basic/Translational Science, chaired by Dr. Xiao-Jing Wang and Dr. Nicholas Mitsiades; and Friday, Session IV – Clinical Research, chaired by Dr. Megan Daly. Poster sessions will allow cancer focused investigators to highlight their innovative science.

The keynote presentation in Session I, *"The Convergence of COE, PED, and CRTEC in NCI-Designated Cancer Centers while Building Transdisciplinary Research: A Population Scientist's View",* brings renowned scientist Dr. Elena Martinez from UC San Diego. Her research focuses in the areas of epidemiology, molecular epidemiology, and cancer prevention.

Session II will feature a panel on *Advancing Cancer Health Equity through Diverse Workforce Development* with speakers spanning the career continuum at UC Davis: Alexa Morales Arana, MD Candidate; Charlotte Bergheimer, MS, PhD candidate; Valentina Zavala-Cordero, PhD, MSc, Postdoctoral Scholar; Olivia Sattayapiwat, MS, MPH, PhD Candidate. These outstanding cancer investigators will share their experiences and provide insights for aspiring researchers.

The keynote lecture for Session III will be given by Dr. Zihai Li from The Ohio State University, whose research centers around understanding the mechanisms of immune regulation in cancer, and with a focus on developing better cancer immunotherapeutics. His presentation is entitled *Sex Bias and Cancer Immunotherapy: Myth or Fact.*

Our final keynote and the David R. Gandara Lectureship Awardee for Friday's Session IV will be given by Dr. Cathy Eng, who focuses on the development of phase I-III clinical trials using novel therapeutics for colorectal, appendiceal and anal cancer patients. She will speak on *Developing Role of ctDNA in GI Malignancies and the Potential Impact on Patient Care.*

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

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

Sincerely,

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

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Executive Associate Dean for Cancer Programs
Professor, Division of Hematology and Oncology, Department of Internal Medicine
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Professor & Auburn Community Cancer Endowed Chair in Basic Science, Genome Center and Biochemistry and Molecular Medicine

Xiao-Jing Wang, MD, PhD
Chief Science Officer and Associate Director for Basic Science, UCD Comprehensive Cancer Center
Professor and Robert E. Stowell Endowed Chair in Experimental Pathology, Department of Pathology and Laboratory Medicine

Nicholas Mitsiades, MD, PhD
Chief Translational Officer and Associate Director for Translational Research, UC Davis Comprehensive Cancer Center
Professor and Albert Holmes Rowe Chair of Genetics III Endowed Chair, Division of Hematology and Oncology, Department of Internal Medicine

Megan Daly, MD
Interim Associate Director for Clinical Research, UCD Comprehensive Cancer Center
Professor, Department of Radiation Oncology

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AGENDA

	28th Annual Cancer Research Symposium		
	Thursday, October 6, 2022		
Time	**Title**	**Presenter**	**Location**
8–8:30 a.m.	**Breakfast**		Boardroom Foyer
8:30–8:45 a.m.	Introduction and Welcome	**Primo Lara, MD** Director, UC Davis Comprehensive Cancer Center	Goodnight Auditorium, 1100 Cancer Center
	SESSION I: Population Sciences and Health Disparities *Chair: Shehnaz Hussain, PhD, ScM*		
Time	**Title**	**Presenter**	**Location**
8:45–9:30 a.m.	Keynote Presentation: "The Convergence of COE, PED, and CRTEC in NCI-Designated Cancer Centers while Building Transdisciplinary Research: A Population Scientist's View"	**Elena Martinez, PhD** Sam M. Walton Endowed Chair for Cancer Research Professor, Herbert Wertheim School of Public Health and Human Longevity Science Associate Director, Population Sciences, Disparities, and Community Engagement, UC San Diego Moores Cancer Center	Goodnight Auditorium, 1100 Cancer Center
9:30–9:45 a.m.	Q&A		
9:45–10 a.m.	"Some Scientific Contributions to the Epidemiology of Hematological Malignancies by Major Subtypes"	**Alain Monnereau, MD, PhD** Research Program Director, Cancer Registry of Greater California, Public Health Institute	
10–10:05 a.m.	Q&A		
10:05–10:20 a.m.	"Personalized, Pandemic-Proof, Population Health"	**Eric Chak, MD, MPH** Associate Professor, Gastroenterology and Hepatology, UC Davis	
10:20–10:25 a.m.	Q&A		
10:25–10:40 a.m.	"Heat Maps: Trends in Late-Stage Diagnoses of Screen-Detectable Cancers in California Counties, 2000-2018"	**Frances Maguire, PhD, MPH,** Epidemiologist, California Cancer Reporting and Epidemiologic Surveillance (CalCARES) Program, UC Davis Comprehensive Cancer Center, UC Davis Health	
10:40–10:45 a.m.	Q&A		
10:45–11 a.m.	**Break**		

	SESSION II: Diverse Career Development and Education *Chairs: Frederick Meyers, MD and Luis Carvajal-Carmona, PhD*		
Time	**Title**	**Presenters**	**Location**
11–12 p.m.	Panel: "Advancing Cancer Health Equity through Diverse Workforce Development"	**Alexa Morales Arana,** MD Candidate, Academic Research Careers for Medical Doctors (ARC-MD), UC Davis School of Medicine **Charlotte Bergheimer, MS,** PhD Candidate, Public Health Sciences, UC Davis **Valentina Zavala-Cordero, PhD, MSc,** Postdoctoral Scholar, Public Health Sciences; AACR-Genentech Cancer Disparities Research Fellow, UC Davis **Olivia Sattayapiwat,** PhD Candidate, Epidemiology, UC Davis	Goodnight Auditorium, 1100 Cancer Center
12–1:30 p.m.	**Poster Session & Lunch**		Boardrooms, 1101 & 1103 Cancer Center

	SESSION III: Basic and Translational Science *Chairs: Xiao-Jing Wang, MD, PhD and Nicholas Mitsiades, MD, PhD*		
Time	**Title**	**Presenter**	**Location**
1:30–2 p.m.	Keynote Presentation: "Sex Bias and Cancer Immunotherapy: Myth or Fact"	**Zihai Li, MD, PhD** Klotz Memorial Chair in Cancer Research Professor and Founding Director Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center	Goodnight Auditorium, 1100 Cancer Center
2–2:15 p.m.	Q&A		
2:15–2:30 p.m.	"Novel Peptide Vaccines against Labyrinthin for Adenocarcinomas"	**Tianhong Li, MD, PhD** Professor of Clinical Medicine Internal Medicine, Hematology & Oncology	
2:30–2:35 p.m.	Q&A		
2:35–2:50 p.m.	"Causes and Consequences of Genome Instability"	**Jacqueline Barlow, PhD** Associate Professor, Microbiology and Molecular Genetics, UC Davis	
2:50–2:55 p.m.	Q&A		
2:55–3:05 p.m.	**Break**		
3:05–3:20 p.m.	"Targeting Killer within the Tumors for Immunotherapy"	**Jogender Tushir-Singh, PhD** Associate Professor, Medical Microbiology and Immunology, UC Davis	
3:20–3:25 p.m.	Q&A		
3:25–3:40 p.m.	"Genetics, Genomics, and Precision Medicine for Gastric Cancer"	**Luis Carvajal-Carmona, PhD** Chief Diversity Officer and Associate Director for Diversity, Equity, and Inclusive Excellence, UC Davis Comprehensive Cancer Center Professor & Auburn Community Cancer Endowed Chair in Basic Science, Genome Center and Biochemistry and Molecular Medicine, UC Davis	
3:40–3:45 p.m.	Q&A		
End of Day 1			

Friday, October 7, 2022

Time	Title	Presenter	Location
8–9:30 a.m.	**Poster Session and Breakfast**		Boardrooms, 1101 & 1103 Cancer Center
SESSION IV: Clinical Research *Chair: Megan Daly, MD*			
9:30–10 a.m.	**David R. Gandara Lectureship on Developmental Therapeutics:** "Developing Role of ctDNA in GI Malignancies and the Potential Impact on Patient Care"	**Cathy Eng, MD, FACP, FASCO** Professor of Medicine, Hematology and Oncology, David H. Johnson Endowed Chair of Surgical and Medical Oncology, Co-Director GI Oncology, Co-Leader Gastrointestinal Cancer Research Program, Director, Young Adults Cancers Program, Chair, Developmental Research Program GI SPORE, Vanderbilt-Ingram Cancer Center	Goodnight Auditorium, 1100 Cancer Center
10–10:15 a.m.	Q&A		
10:15–10:30 a.m.	"Current Landscape of HCC Treatment: Evolving Fast and Furious (With Some Potholes)"	**Edward Kim MD, PhD** Medical Director, Office of Clinical Research, UC Davis Comprehensive Cancer Center Associate Professor, Hematology and Oncology, UC Davis	
10:30–10:35 a.m.	Q&A		
10:35–10:50 a.m.	"Immunotherapy for Colorectal Cancer: Successes and Setbacks"	**Arta Monjazeb, MD, PhD** Professor, Radiation Oncology, UC Davis	
10:50–10:55 a.m.	Q&A		
10:55–11:05 a.m.	**Break**		
11:05–11:20 a.m.	"Define Synergism Correctly: A New PK-PD Model for Combination Therapy"	**Aiming Yu, PhD** Director, Molecular Pharmacology Shared Resource Professor, Biochemistry and Molecular Medicine, UC Davis	
11:20–11:25 a.m.	Q&A		
11:25–11:40 a.m.	"Parametric PET of Liver Inflammation and Its Implications for Cancer Immunotherapy"	**Guobao Wang, PhD** Associate Professor, Radiology, UC Davis	
11:40–11:45 a.m.	Q&A		
11:45–11:55 a.m.	Closing Remarks and Poster Awards Announcement	**Primo Lara, MD** Director, UC Davis Comprehensive Cancer Center	
Symposium Close			

ORAL PRESENTATIONS

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

Dr. Martinez is an epidemiologist with expertise in cancer and cancer disparities research. She is currently Professor in the Herbert Wertheim School of Public Health and Human Longevity Science and Associate Director of Population Sciences, Disparities and Community Engagement at UC San Diego's Moores Cancer Center. She is currently President of the American Society for Preventive Oncology. She is Lead Principal Investigator (PI) of the NIH-funded SDSU/UCSD Cancer Center Comprehensive Partnership, whose mission is to address cancer disparities in Hispanic/Latino populations through research, research education, and community outreach. She is lead PI of the Accelerating Colorectal Cancer Screening and Follow-up through Implementation Science Cancer Moonshot grant, which addresses the extremely low colorectal cancer screening and follow-up rates in community health centers in San Diego County. She is MPI of the California Teachers Study, a NCI-funded cohort study. Nationally, she has established strong leadership and commitment to the area of cancer health disparities, particularly in relation to Hispanic/Latino populations in the U.S. She has served on NCI's Board of Scientific Counselors and Board of Scientific Advisors. Finally, she was one of 28 members nationally who served on the prestigious Cancer Moonshot Blue Ribbon Panel. Dr. Martinez is highly committed to training the next generation of cancer scientists, particularly those from under-represented groups and those whose research focuses on disparities and equity.

Elena Martinez, PhD
Sam M. Walton Endowed Chair for Cancer Research, Professor, Herbert Wertheim School of Public Health and Human Longevity Science, Associate Director, Population Sciences, Disparities, and Community Engagement, UC San Diego Moores Cancer Center

Zihai Li, MD, PhD
Klotz Memorial Chair in Cancer Research, Professor and Founding Director Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center

Dr. Zihai Li is an American Board of Internal Medicine-certified medical oncologist, cancer immunologist, elected member of the American Society of Clinical Investigation, the Association of American Physicians, and a fellow of the American Association for the Advancement of Science. He is the Klotz Memorial Chair in Cancer Research, Professor and Founding Director of the Pelotonia Institute for Immuno-Oncology at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute. An expert in the field of GP96/GRP94 chaperone biology, Li established its roles in immunity, development, and cancer by advancing the knowledge of its client network, structure-function relationship, and its co-chaperone CNPY3. He uncovered the roles of the TGFβ-GARP axis and platelets in immune tolerance and cancer immunotherapy and discovered CNPY2 as a key initiator of the unfolded protein response. More recently, he is credited for his work in linking androgen receptor and CD8+ T cell exhaustion in the tumor as one of the bases for sex bias in cancer. Much of his ongoing research centers around understanding the mechanisms of immune regulation in cancer, and with a focus on developing better cancer immunotherapeutics. He has authored over 180 manuscripts on these topics. His laboratory has been continuously funded by the National Institutes of Health for the last two decades with a total funding of over $26 million.

A passionate educator and mentor, Li has trained more than 60 graduate students, post-doctoral fellows, and junior faculty members. Li earned his medical degrees from Zhengzhou University and Peking Union Medical College, and his PhD in immunology with Dr. Pramod Srivastava from the Icahn School of Medicine at Mount Sinai in 1993. He completed his internal medicine residency in the Montefiore-Einstein Medical Center and his medical oncology fellowship at the Fred Hutchinson Cancer Research Center and University of Washington.

Dr. Eng, Professor of Medicine, Hematology and Oncology, is the David H. Johnson Endowed Chair of Surgical and Medical Oncology, Co-Director of GI Oncology and the Co-Leader of the Gastrointestinal Cancer Research Program, Director of the new Young Adults Cancers Program, and the Chair, Developmental Research Program for the GI SPORE, at the Vanderbilt-Ingram Cancer Center. She served as the Ambassador for the American Cancer Society ResearcHERS campaign in Nashville (2020-2022). She is currently the Director for Strategic Relations for Vanderbilt-Ingram Cancer Center. She has served on the Scientific Review Committee and remains on the Clinical Trials Shared Resource Oversite Committee. She is a highly sought mentor and served on the Vanderbilt-Ingram Mentorship Council and is currently a mentor on the T-32 grant and serves as a Professional Development Mentor. She continues to assume leadership positions devoted to clinical research. She has focused on the development of phase I-III clinical trials using novel therapeutics for biomarker discovery and enhanced drug utilization in colorectal, appendiceal and anal cancer patients.

Cathy Eng, MD, FACP, FASCO, Professor of Medicine, Hematology and Oncology, David H. Johnson Endowed Chair of Surgical and Medical Oncology, Co-Director GI Oncology, Co-Leader Gastrointestinal Cancer Research Program, Director, Young Adults Cancers Program, Chair, Developmental Research Program GI SPORE, Vanderbilt-Ingram Cancer Center

Nationally, Dr. Eng has also been highly active serving on ASCO, ECOG, and SWOG. She has served on multiple committees for ASCO including the Career Development Committee, Education Committee for Colorectal Cancer; ASCO Scientific Program Committee Track Leader for the Gastrointestinal Cancer-Colorectal/Liver Track and served on the Steering Committee 2012-2015. She is the former Chairman of the Scientific Program Committee of the ASCO Gastrointestinal Cancer Symposium from 2012-2013 and Chairman, Steering Committee, GI Cancers Symposium 2016. She was chosen for the ASCO Leadership Development Program and served on the ASCO Government Relations Committee; worked with the ASCO Cancer Prevention Committee on the consensus statement regarding HPV vaccination; served on the ASCO Nausea and Vomiting Guidelines Committee, ASCO Taxonomy Task Force, ASCO Social Media Committee, and is currently on the ASCO Colorectal Guidelines Committee, ASCO Scientific Program Committee (Colorectal Cancer Track) and the ASCO Communications Committee. She was the co-chair of the SWOG Rectal/Anal Cancer Subcommittee and was the Vice-Chair for the SWOG GI Committee. She was the Chairman of the NCI Rectal/Anal Task Force (two terms), served on the NCI GI Steering Committee, and is now the co-Chair of the NCI GI Steering Committee.

She has published in many peer reviewed journals including Journal of Clinical Oncology, Lancet Oncology, Nature Review, JNCI, Annals of Oncology, Cancer, and Annals of Surgical Oncology. She has previously received an NCI grant "Administrative Supplements to the institutional CCSG grant to Support Biomarker Studies Associated with NCI-supported Clinical Trials of Immunotherapy". She was a co-PI for the MD Anderson Moonshot for HPV-Associated Malignancies (Section Lead for the Rare Cancers subsection) and continues to serve as a grant reviewer on the MD Anderson Colorectal Cancer Moonshot Grant and the Sabine award. She has served as a consultant to the FDA and AHRQ, Cancer Research UK: Training & Career Development Board - Clinician Scientist Fellowship, the Italian Association for Cancer Research, the Dutch Digestive Foundation, the Stand Up to Cancer (SU2C) - Farrah Fawcett Foundation Joint Scientific Advisory Committee (JSAC) and the SWOG Impact Award. She currently serves on the Vanderbilt University Medical Center, T-32 Internal Advisory Council.

ABSTRACTS OF ORAL PRESENTATIONS (THURSDAY)

SESSION I: Populations Sciences and Health Disparities
Chair: Shehnaz K Hussain, PhD, ScM

KEYNOTE LECTURE: THE CONVERGENCE OF COE, PED, AND CRTEC IN NCI-DESIGNATED CANCER CENTERS WHILE BUILDING TRANSDISCIPLINARY RESEARCH: A POPULATION SCIENTIST'S VIEW

Elena Martinez, PhD, Sam M. Walton Endowed Chair for Cancer Research, Professor, Herbert Wertheim School of Public Health and Human Longevity Science Associate Director, Population Sciences, Disparities, and Community Engagement, UC San Diego Moores Cancer Center

Requirements for NCI designation of Cancer Centers have recently increased and continue to evolve. Centers serve as major sources of discovery and of the development of more effective approaches to cancer prevention, diagnosis, and therapy. Integrating meritorious collaborate transdisciplinary research in the recently added components of Community Outreach and Engagement, Cancer Research Training and Education Coordination, and ensuring a diverse membership has become a challenge for all Cancer Centers. This presentation will provide a Population Scientist's view of this challenge and provide possible solutions using experience and lessons learned.

SOME SCIENTIFIC CONTRIBUTIONS TO THE EPIDEMIOLOGY OF HEMATOLOGICAL MALIGNANCIES BY MAJOR SUBTYPES

Alain Monnereau, MD, PhD, Research Program Director, Cancer Registry of Greater California, Public Health Institute

The aim of my talk is to bring to the audience some examples from my research on the epidemiology of hematological malignancies (HM) and the benefit of studying HM's subtypes. Examples will be given about population-based incidence or survival studies, as well as a past international initiative on lymphoma subtypes that pooled 20 case-control studies to distangle etiological factors. More recent ongoing initiatives will be discussed like the « Real World dAta in Lymphoma and Survival in Adult » cohort (REALYSA) or the study in collaboration with the French National Geographic Institute on passive residential environmental exposure to agricultural pesticides and HM risk in the general population.

PERSONALIZED, PANDEMIC-PROOF, POPULATION HEALTH

Eric Chak, MD, MPH, Gastroenterology and Hepatology, UC Davis

Older individuals are at particularly high risk for solid malignancy and vaccine preventable illness. As such, the United States Preventive Services Task Force (USPSTF) and Centers for Disease Control and Prevention (CDC) have published guidelines to maximize their well-being. We report the results of "Enhancing Electronic Health Systems to Decrease the Burden of Colon Cancer, Lung Cancer, Obesity, Vaccine-Preventable Illness, and LivER Cancer" (CLOVER), an application of electronic population health tools which were tailored to increase uptake of preventive health services, especially cancer screenings and vaccinations, among older adults during the COVID-19 pandemic.

HEAT MAPS: TRENDS IN LATE-STAGE DIAGNOSES OF SCREEN-DETECTABLE CANCERS IN CALIFORNIA COUNTIES, 2000-2018

Frances Maguire PhD, MPH, Epidemiologist, California Cancer Reporting and Epidemiologic Surveillance (CalCARES) Program, UC Davis Comprehensive Cancer Center, UC Davis Health

Seven types of cancer have potential for early diagnosis through screening including female breast, colorectal, cervical, prostate, melanoma, oropharyngeal, and lung cancers. Using data from the California Cancer Registry, we created heat maps showing changes over time in late-stage diagnoses for these seven cancer types by California county. We used linear regression to determine trends and to assess whether increases or decreases were statistically significant. In the most recent 10-year period, late-stage diagnoses have significantly increased for colorectal and prostate cancers; significantly decreased for melanoma and lung

cancers; and remained relatively constant for breast, cervical, and oropharyngeal cancers. We found regional and county level differences in late-stage diagnoses.

Session II: Diverse Career Development and Training

Chair: Frederick Meyers, MD, MACP and Luis Carvajal-Carmona, PhD

PANEL: ADVANCING CANCER HEALTH EQUITY THROUGH DIVERSE WORKFORCE DEVELOPMENT

Alexa Morales Arana, MD Candidate, Academic Research Careers for Medical Doctors (ARC-MD)
Alexa Morales Arana is a first-year medical student at UC Davis School of Medicine and is a part of the Academic Research Careers for Medical Doctors (ARC-MD) program. She is interested in cancer research and precision medicine to address cancer health disparities among US racial/ethnic minority communities.
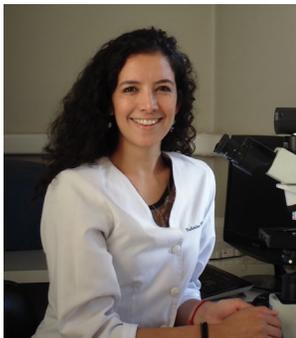
Charlotte Bergheimer, MS, PhD candidate, Public Health Sciences
Charlotte is a doctoral student in Public Health Sciences at the University of California, Davis and has over a decade of experience working to improve health outcomes and reduce disparities in underserved communities. Before returning to school, she developed and managed National Cancer Institute-supported clinical trials for Children's Oncology Group, and taught Nutrition part-time at Cal State Northridge and Cal Poly Pomona. Charlotte serves as Chair of the Board of Directors for the statewide food policy organization Nourish California, and her research focuses on program implementation and health behavior change in low-income communities. With her PhD, Charlotte hopes to support evidence-based policy and practice transformation to improve cancer health disparities related to nutrition access.

Valentina Zavala-Cordero, PhD, MSc, Postdoctoral Scholar, Public Health Sciences; AACR-Genentech Cancer Disparities Research Fellow
Dr. Zavala earned her doctorate in molecular and cellular biology at Pontificia Universidad Católica of Chile, studying the effect of up-regulated microRNAs on BRCA1 expression in breast cancer. In 2018, she joined Laura Fejerman's lab at University of California, San Francisco, where she was trained in integrative genomics through the study of the genetic factors that contribute to breast cancer risk in Latinas. In 2020, she moved to the University of California, Davis, where she continues her research focusing on understanding the molecular mechanisms that link population-specific genetic variants to breast cancer biology in Latinas. In 2021, Dr. Zavala was granted the AACR-Genentech Cancer Disparities Research Fellowship to study the functional effect of Indigenous American breast cancer-risk germline variants.

Olivia Sattayapiwat, MS, MPH, PhD Candidate, Epidemiology
Olivia Sattayapiwat is a PhD candidate in the Graduate Group of Epidemiology program. Her research interests lie mainly in cancer epidemiology, working to improve identification and measurement of risk factors to build better cancer risk prediction models and target interventions. Her thesis research focuses on advancing our understanding of the associations between specific benign breast disease diagnoses and future breast cancer risk. Prior to joining UC Davis, Olivia received her MPH in Environmental Health Sciences from UCLA, and her Master's degree in Epidemiology from USC. Between earning her MPH and MS degrees, Olivia worked as a data analyst at the Breast Diagnostic Center at Torrance Memorial Medical Center, and then as a research associate in the research department at Kaiser Permanente Southern California, supporting cancer epidemiology studies related to prostate, non-Hodgkin's lymphoma, adolescent and young adult, bladder, ovarian, and breast cancer.

SESSION III: Basic/Translational Science
Chair: Xiao-Jing Wang, MD, PhD and Nicholas Mitsiades, MD, PhD

KEYNOTE LECTURE: SEX BIAS AND CANCER IMMUNOTHERAPY: MYTH OR FACT

Zihai Li, MD, PhD, Klotz Memorial Chair in Cancer Research, Professor and Founding Director Pelotonia Institute for Immuno-Oncology, The Ohio State University Comprehensive Cancer Center

Sex, as organized by the unequal composition and effects of sex chromosomes and gonadal hormones, is a biological variable with substantial influence on immune function. Pan cancer analyses also reveal more mutation burdens in male comparing with female, suggesting that effectiveness of immune surveillance might have a sex bias. We have recently visited this question using pre-clinical models. We unexpectedly discovered that androgen receptor expressed on T cells has important cell intrinsic roles in promoting CD8+ T cell dysfunction in the tumor microenvironment. I will discuss this finding in the broader context of cancer immunotherapy especially with anti-PD1/PD-L1 based immune checkpoint blockers.

NOVEL PEPTIDE VACCINES AGAINST LABYRINTHIN FOR ADENOCARCINOMAS

Tianhong Li, MD, PhD[1],[2], [1]Division of Hematology/Oncology, Department of Internal Medicine, University of California Davis School of Medicine, University of California Davis Comprehensive Cancer Center, Sacramento, CA, USA; [2]Medical Service, Hematology and Oncology, Veterans Affairs Northern California Health Care System

Labyrinthin (Laby) is a new tumor-specific protein expressed on the surface of most adenocarcinomas. We developed an immunohistochemistry (IHC) assay to detect Laby expression on archived patient tumors, and showed Laby expression was associated with poor prognosis. LabVax 3(22)-23 is a novel tumor vaccine that contains 4 synthetic labyrinthin-based peptides designed to elicit both B-cell and T-cell responses. LabVax 3(22)-23 in combination with pembrolizumab significantly inhibited the growth of murine MC-38-huPD-L1 tumors in C57/BL6 transgenic mice expressing human PD-1/PD-L1. Preliminary data from the ongoing, single institution, first-in-human phase I trial (UCDCC#296, NCT051013560) evaluating LabVax 3(22)-23 and adjuvant sargramostim in patients with refractory metastatic or recurrent adenocarcinoma of any primary tumor site will be presented.

CAUSES AND CONSEQUENCES OF GENOME INSTABILITY

Jacqueline Barlow, PhD, Associate Professor, Microbiology and Molecular Genetics, UC Davis

Replication is a potent source of DNA damage and chromosome rearrangements in proliferating cells, and likely plays an important role in the initiation and evolution of cancer. Different forms of replication stress induce distinct types of DNA rearrangements: the DNA polymerase inhibitor aphidicolin (APH) and crosslinking agent cisplatin induce radial chromosome fusions, a hallmark of multiple cancer predisposition syndromes. Using small molecule inhibitors to DNA repair kinases and repair factors, we find that replication stress-induced radial chromosome formation relies on an active ATR-Chk checkpoint kinase cascade, as well as the homologous recombination protein Rad51. We conclude that radial chromosomes are products of aberrant homologous recombination-mediated repair. We propose monitoring radial chromosome formation is a potential mode to measure the effectiveness of targeted cancer therapies.

TARGETING KILLER WITHIN THE TUMORS FOR IMMUNOTHERAPY

Jogender Tushir-Singh, PhD, Associate Professor, Medical Microbiology and Immunology, UC Davis

Over the past decade, multiple death receptor-5 (DR5) antibodies have moved to phase-I and phase-II clinical trials after successfully controlling tumors in animal models. On the contrary, despite the high expression and well-established role of another death receptor named Fas receptor (FasR) in promoting tumor growth, not a single Fas antibody has made it to clinical trials. The latter is due to apparent concerns of potential bystander cytotoxicity to immune effector T and NK cells, as they also respond to Fas signaling for immune homeostasis. Via pursuing our recent discovery of the DR5 autoinhibitory ectodomain, we have engineered a novel FasR antibody. Our preliminary results indicate the selective death of tumor cells by the lead FasR antibody without harming the immune-effector cells.

GENETICS, GENOMICS, AND PRECISION MEDICINE FOR GASTRIC CANCER

Luis Carvajal-Carmona, PhD, *Chief Diversity Officer and Associate Director for Diversity, Equity, and Inclusive Excellence, UC Davis Comprehensive Cancer Center, Professor & Auburn Community Cancer Endowed Chair in Basic Science, Genome Center and Biochemistry and Molecular Medicine, UC Davis*

I will present an overview of gastric cancer epidemiology with an emphasis on genetic risk and will describe results from several studies in the Carvajal-Carmona lab that are advancing health equity research across the gastric cancer continuum.

ABSTRACTS OF ORAL PRESENTATIONS (FRIDAY)

SESSION IV: Clinical Research
Chair: Megan Daly, MD

<u>DAVID R. GANDARA LECTURESHIP ON DEVELOPMENTAL THERAPEUTICS</u>: DEVELOPING ROLE OF ctDNA IN GI MALIGNANCIES AND THE POTENTIAL IMPACT ON PATIENT CARE

Cathy Eng, MD, FACP, FASCO, David H. Johnson Endowed Chair in Surgical and Medical Oncology; Professor of Medicine, Hematology and Oncology; Director for Strategic Relations; Co-Director, GI Oncology; Co-Leader, Gastrointestinal Cancer Research; Director, Young Adult Cancers Program; Co-Chair, NCI GI Steering Committee, Vanderbilt-Ingram Cancer Center

Noninvasive approaches have been sought for several years to assist in the care of gastrointestinal malignancies as well as other malignancies. As of late, the role of circulating tumor DNA has been noted to have a potential role in early stage colon cancer as a prognostic indicator. Yet to date, the consideration of circulating tumor DNA remains investigational in metastatic colon cancer and in other GI alignancies. Several clinical trials are ongoing and will be discussed. A general overview regarding the role of ctDNA to date will be provided as well as a review of the existing literature and the potential role of ctDNA as a standard of care will be provided.

CURRENT LANDSCAPE OF HCC TREATMENT: EVOLVING FAST AND FURIOUS (WITH SOME POTHOLES)

Edward Kim MD, PhD, Medical Director, Office of Clinical Research, UC Davis Comprehensive Cancer Center, Associate Professor, Hematology and Oncology, UC Davis

Over past 5 years, the number of systemic treatment options for advanced hepatocellular carcinoma has increased at a remarkable rate. For almost a decade, sorafenib remained the only systemic treatment option. In just the past 5 years, several new monotherapy options have emerged adding multiple lines of therapy. Dual therapy options have also been developed further moving the needle by demonstrating significant improvements in outcomes. The rapid change in treatment options has ushered in a new era of systemic treatment for HCC but has created unique new challenges including determining optimal sequencing of these new options and execution of clinical trials in the context of this shifting landscape. In addition, areas of unmet need remain including a large portion of HCC patients with underlying liver function that does not meet the criteria used for all HCC trials. Updates on recent research in this space at UC Davis CCC will be highlighted.

IMMUNOTHERAPY FOR COLORECTAL CANCER: SUCCESSES AND SETBACKS

Arta Monjazeb, MD, PhD, Professor, Radiation Oncology, UC Davis

The efficacy of immunotherapy in colorectal cancer (CRC) has demonstrated both the power and limitations of this approach. In microsatellite instable (MSI-high) CRC there has been tremendous success of immune checkpoint inhibitors (ICI) which has completely revolutionized the clinical care of these patients. Conversely in MSI-low CRC ICI immunotherapy has failed to make an impact. This has led many to incorrectly assume that MSI-low CRC lacks an immune permissive tumor microenvironment (TME). However the immunoscore concept was first developed in CRC which can have extensive lymphocyte infiltrates as well as relatively high mutational burden. Thus, the failure of ICI in MSI-low CRC remains a mystery. We will explore trials examining immunotherapy in CRC as well as potential immunotherapy strategies for MSI-low CRC.

PARAMETRIC PET OF LIVER INFLAMMATION AND ITS IMPLICATIONS FOR CANCER IMMUNOTHERAPY

Guobao Wang, PhD, Associate Professor of Radiology, UC Davis

Chronic inflammation of the liver may lead to advanced liver disease and impair the immune system. Clinical imaging of liver inflammation is nontrivial. We have developed a parametric positron emission tomography (PET) imaging method based on a glucose transport hypothesis and validated the method in nonalcoholic fatty

liver disease which is the most common type of chronic liver disease and an independent risk factor for several gastrointestinal cancers. The enabled PET imaging of liver inflammation may have several implications in immunotherapy of gastrointestinal malignancies, including nonalcoholic steatohepatitis-related hepatocellular carcinoma and other gastrointestinal cancers with liver metastasis.

DEFINE SYNERGISM CORRECTLY: A NEW PK-PD MODEL FOR COMBINATION THERAPY

Aiming Yu, PhD, *Director, Molecular Pharmacology Shared Resource Professor, Biochemistry and Molecular Medicine, UC Davis*

Understanding pharmacokinetic-pharmacodynamic (PK-PD) relationship is critical in drug development and clinical therapy. As combination therapy is common, searching for a synergistic combination is warranted. However, conventional PK-PD models do not recognize quantitative contributions from individual drugs, and "interaction factor" is misused to define pharmacologic synergism *in vivo*. In this talk, I will clarify the definition of synergism and highlight proper means to determine synergism. I will further present a novel PK-PD model for combination therapy by considering apparent contributions from individual drugs or mutual interactions, as well as the incorporation of combination index method to critically determine *in vivo* synergism.

POSTER PRESENTATIONS

Thursday poster session: 12:00 pm – 1:30 pm

Friday poster session: 8:00 am – 9:30 am

THURSDAY POSTER PRESENTATIONS (INDEX)

1. **Biology of Breast Cancer Subtypes for Peruvians**
   Presenter: Cassie (Chenghuiyun) Xu

2. **Effect of Latency Time and Primary Tumor Type on Secondary Breast Cancer Survival by Age**
   Presenter: Candice Sauder

3. **Evaluation and Improvement of Previously Reported Polygenic Risk Scores for Breast Cancer in Peruvian Women**
   Presenter: Xiaosong Huang

4. **Factors Associated with Emergency Department Use, Timeliness and Access of Health Care in Older Adults with Leukemia and Lymphoma**
   Presenter: Alex Fauer

5. **Guideline-Congruent Care is Associated with Increased Survival Among Adolescents and Young Adults with Primary Mediastinal Germ Cell Tumors: A Population-Base Study**
   Presenter: Renata Abrahão

6. **Linking the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry to the California Cancer Registry and California Hospital Patient Discharge Data**
   Presenter: Ann Brunson

7. **Activation of Neural Lineage Networks and ARHGEF2 in Enzalutamide-Resistant and Neuroendocrine Prostate Cancer Cells and Association with Patient Outcomes**
   Presenter: Shu Ning

8. **Characterization of Intermediate Filament Assemblies Through Solid State NMR**
   Presenter: Kayla Osumi

9. **Characterizing Cellular Topography and Molecular Signatures of Immune Cell Populations in the Canine Brain**
   Presenter: Christine Toedebusch

10. **Circadian Clock and Metabolic Regulator Rev-Erbβ Controls Androgen Receptor Signaling in Prostate Cancer**
    Presenter: Xingling Zheng

11. **Does Burning Fat Make Tumor Immune Hot? FAO Enhances Tumor Growth with Immune Evasion**
    Presenter: Jian Jian Li

12. **EN1 as a Potential Indicator of Metastatic Progression in Pancreatic Cancer**
    Presenter: Thae Su Thu

13. **Engrailed-1 Promotes Pancreatic Cancer Progression and Metastasis**
    Presenter: Reno Jihao Xu

14. **Epigenetic Regulator Histone Methyltransferase G9a Drives NEPC Progression through Promoting Neuronal Lineage Differentiation**
    Presenter: Xiong Zhang

15. **Inhibition of Phospholipase D1 Reduces Pancreatic Carcinogenesis in Mice**
    Presenter: Hala Addassi

16. **Metabolism-Master Regulator SREBP2 Reactivates Developmental Program in Triple-Negative Breast Cancer**
    Presenter: Yatian Yang

17. **Molecular and Histological Characterization of Two Genetically Engineered Mouse Models of Non-Small Cell Lung Cancer**
    Presenter: Nicole Leon

18. **Targeting Metabolic Addiction and DNA Repair of Therapy-Resistant Prostate Cancer**
    Presenter: Leandro D'Abronzo

19. **GigaFIBI; Rapid, Large-Format Histology-Resolution Imaging for Intraoperative Assessment of Breast Lumpectomy Margins**
    Presenter: Farzad Fereidouni

20. **Modification of Hyaluronic Acid for CD44 and Integrin αvβ6 Dual Targeting and Radio-Labeling**
    Presenter: Hua Zhang

21. **A pH-Driven Small-Molecule Nanotransformer Hijacks Lysosomes and Overcomes Autophagy-Induced Resistance in Cancer**
    Presenter: Menghuan Tang

22. **An Exceptional Tumor Response to Novel CTLA-4 Inhibitor ONC-392 in a Patient with Refractory Adenoid Cystic Carcinoma: A Case Report from an Ongoing Clinical Trial**
    Presenter: Varun Viswanath

23. **An Integrated Multidisciplinary Evaluation Platform and Early Experience for Precision Therapy in Resectable NSCLC**
    Presenter: Joy Chen

24. **An Integrin αvβ6 Binding Peptide-Drug-Conjugate for Tumor Targeted Drug Delivery**
    Presenter: Ryan Davis

25. **ARID1A Alterations as Positive Predictors of Immune Checkpoint Inhibitor Efficacy in Advanced Non-Small Cell Lung Cancer: Real World Data Analysis**
    Presenter: Ebaa Al-Obeidi

26. **Assessing Systemic and Local Levels of Lidocaine During Surgery for Glioblastoma**
    Presenter: Robert Riestenberg

27. **Bioengineering Novel siRNA Agents for Cancer Research via in vivo Fermentation**
    Presenter: Neelu Batra

28. **Characterization of Natural Killer and Cytotoxic T Cell Immune Infiltrates in Osteosarcomas**
    Presenter: Julia Persky

29. **High Labyrinthin Expression is Associated with Poor Prognosis in Patients with NSCLC**
    Presenter: Jie Zeng

30. **Human Soft Tissue Sarcomas Harbor an Intratumoral Viral Microbiome Which is Linked with Natural Killer Cell Infiltrate and Prognosis**
    Presenter: Sylvia Cruz

31. **IGFBP3 Promotes Resistance to Olaparib via Modulating EGFR Signaling in Advanced Prostate Cancer**
    Presenter: Amy Leslie

32. **Quantifying and Identifying DNA Adducts of Carcinogens and Therapeutics**
    Presenter: Bruce Buchholz

FRIDAY POSTER PRESENTATIONS (INDEX)

1. **Methodology Matters: A Comparison Between Mail-In Surveys and Community Outreach Efforts when Capturing Latino Health Responses in an NCI Designated Catchment Area**
Presenter: April Vang

2. **Racial/Ethnic Disparities in Receipt of Guideline-Congruent Care and Survival Among AYA Patients with Testicular Germ Cell Tumors**
Presenter: Fran Maguire

3. **Regulation of Genes Located in 6q25 by an Indigenous American Genetic Variant in Breast Cancer Patients from Peru**
Presenter: Valentina Zavala-Cordero

4. **Survival After Contralateral Secondary Breast Cancer by Age Group in California**
Presenter: Lauren Perry

5. **Force-Induced Accumulation of Tensin and LIM Proteins Along Keratin Fibers**
Presenter: Karen Zhao

6. **Investigating Core Binding Factor Beta's Role in Protein Translation in Osteosarcoma**
Presenter: Nick Oldberg

7. **Mesenchymal Stem/Stromal Cell Effects on Neuroblastoma Cells Growth**
Presenter: Erin Brown

8. **Natural Compounds Ursolic Acid and Digoxin Exhibit Anti-Cancer Effects Through Nuclear Receptor RORγ-Dependent and -Independent Mechanisms**
Presenter: Hongye Zou

9. **Olfactomedin-like 3 Promotes Malignant Reatures of Patient-Derived Glioblastoma Cell Lines**
Presenter: Shafee Syed-Quadri

10. **Pre-Clinical Evaluation and First-in-Dog Clinical Trials of Intravenous Infusion of PBMC-Expanded Adoptive NK Cell Therapy in Dogs with Cancer**
Presenter: Aryana Razmara

11. **Low-dose Sorafenib Enriches for Cancer Stem Cells and is Associated with Accelerated Tumor Progression in Soft Tissue Sarcomas**
Presenter: Khurshid Iranpur

12. **Role of BHLHE40 in Therapy-Resistant Prostate Cancer**
Presenter: Kristina Wells

13. **The C-type Lectin Domain of CD62P (P-selectin) Interacts with Integrins and Potentially Mediates Cancer Cell-Endothelium Interaction, an Initial Step in Cancer Metastasis.**
Presenter: Yoshikazu Takada

14. **The Impact of Metals on the Structure and Dynamics of the Tail Domain of Vimentin**
Presenter: Estely Carranza

15. **Intraoperative Detection of IDH-Mutant Glioma Subtype Using Fluorescence Lifetime Imaging**
Presenter: Silvia Noble Anbunesan

16. **The Role of Interventional MRI for Selective Drug Delivery in Brain Cancer**
Presenter: Felipe Godinez

17. **A Pilot Study on Retinal Features and Cognitive Function in Patients with Low Grade Gliomas**
Presenter: Yin Allison Liu

18. **A Western-Style Mimicking High-Fat Diet Increases Early Stage Pancreatic Carcinogenesis in a KC Murine Model**
Presenter: Aya Ead

19. **Bioengineering MicroRNAs to Modulate Solute Carrier Transporters**
Presenter: Colleen Yi

20. **Development of a Simple and Reproducible Cell-Derived Orthotopic Xenograft Murine Model for Neuroblastoma**
Presenters: Kathleen Doyle and Abdul Hassan

21. **Functional Genetics of APR-246 Rescuable TP53 Mutants**
Presenter: Anais Saunders

22. **Functional Outcomes of Lip-Split Mandibulotomy for Access of Oral and Oropharyngeal Tumors**
Presenter: Anastasiya Stasyuk

23. **Immune Modeling of Colorectal Liver Metastases (CRLM) Using an Ex-Vivo 3D Tumor-on-a-Chip Model**
Presenter: Sepideh Gholami

24. **Incidence of Intracranial Hemorrhage in Glioma Patients with Venous Thromboembolism Converted from LMWH to Apixaban**
Presenter: Orwa Aboud

25. **Novel Bioengineered miR-1291 Modulates the Expression of Xenobiotic Nutrient Transporters and Metabolic Enzymes to Control Cancer Cell Metabolism**
Presenter: Meijuan Tu

26. **Novel HSP70 Inhibitors Improve Enzalutamide Treatment in Prostate Cancer**
Presenter: Pengfei Xu

27. **Osteotropic Regulation of Bhlhe40 in Bone**
Presenter: Damian Genetos

28. **Receptor Tyrosine Kinase (RTK)/ALK Inhibitor Alectinib Blocks Neuroendocrine Prostate Cancer Cell Growth**
Presenter: Eric Arreola

29. **Role of miR-7-5p in Mitochondrial Function**
Presenter: Gavin Traber

30. **Salmeterol Xinafoate Preferentially Eradicates Glioma Cells, In Vitro**
Presenter: Orli Algranatti

31. **Evaluation of Cytotoxicity, Safety and Mammary Tissue Retention of Thermosensitive Systems Containing Nanostructured Lipid Carriers for Co-Administration of Paclitaxel and Tributyrin as a New Strategy for the Localized Treatment of Breast Cancer**
Presenter: Julia Sapienza Passos

THURSDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>>   BIOLOGY OF BREAST CANCER SUBTYPES FOR PERUVIANS

Cassie (Chenghuiyun) Xu, PhD Candidate in the Graduate Group of Biostatistics
Valentina A. Zavala[1], Xiaosong Huang[1], Sandro Casavilca-Zambrano[2], Jeannie Navarro-Vásquez[2], Carlos A. Castañeda[2], Guillermo Valencia[2], Zaida Morante[2], Monica Calderón[2], Julio E. Abugattas[2], Henry Gómez[2], Hugo A. Fuentes[2], Ruddy Liendo-Picoaga[2], Jose M Cotrina[2], Silvia P. Neciosup[2], Katia Roque[2], Jule Vásquez[2], Luis Mas[2], Marco Gálvez-Nino[2], Jovanny Zabaleta[3], Tatiana Vidaurre[2*], David M. Rocke[1,5], Laura Fejerman[1,4]
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Breast cancer incidence and outcomes differ by US census racial/ethnic category. Since large-scale genetic studies of human disease are predominately focused on populations of European ancestry, little is known about breast cancer molecular biology in Hispanic/Latinos. This lack of knowledge due to the absence of diverse genetic data and bio-specimens can widen cancer health disparities due to suboptimal translation of discoveries into clinical practice or public health policy. In this study we aim to describe relevant pathways in breast cancer subtype differentiation in breast cancer patients from Peru. The Peruvian Breast Cancer Genomics Study (PEGEN-BC) recruited ~2000 women with breast cancer at the Instituto Nacional de Enfermedades Neoplásicas (INEN) in Lima, Peru. Formalin fixed paraffin embedded tumor tissues samples were whole exome sequenced for a total of 271 patients. Intrinsic tumor subtypes were classified using the PAM50 method and pathway comparison between subtypes was conducting using GSEA. We estimated the median Indigenous American ancestry proportions for participants using germline genome wide genotypes and the program Admixture. The mean age of patients with available RNA seq data was 50 and the median Indigenous American ancestry was 79%. We found that most of the significantly changed pathways were similar to previous findings in the literature while there were some exceptions. For example, when comparing the luminal A and basal subtype, we found that the Peruvian tumors showed the glycolysis and heme metabolism as significantly changed. Future research will further explore the differential pathways and assess possible implications linked to etiology or prognosis.

<<2>>   EFFECT OF LATENCY TIME AND PRIMARY TUMOR TYPE ON SECONDARY BREAST CANCER SURVIVAL BY AGE

Candice Sauder[1,2], Qian Li [3], Fran Maguire [4], Kathryn Ruddy [5], Theresa Keegan [1,3]
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Background: Secondary cancers account for 16% of cancer diagnoses, with breast cancer (BC) being the most common. Compared to primary BC, secondary breast cancer (sBC) has unique characteristics and decreased survival, but the impact of latency or primary tumor type on breast cancer-specific survival (BCSS) in sBC is unknown.

Methods: Females diagnosed with sBC, with a prior primary tumor of any type, during 1991-2015 (n=37,625) were obtained from the California Cancer Registry. We assessed the impact of latency (<2, 2-<5, 5-<10, ≥10

years) and primary cancer type on BCSS by age group (≤50 years, younger; >50, older) using multivariable Cox proportional hazards regression.

Results: Most older women developed sBC >5 years after primary cancer (61.1%), whereas most younger women developed sBC within 5 years (53.9%), with few after 10 years (16.5%). Older women with sBC tended to have lower stage tumors, be less likely to get chemotherapy or mastectomies, and be hormone receptor positive than younger women. BCSS was decreased for younger (hazard ratio (HR)=1.42, 95% confidence interval (CI): 1.27-1.59) and older (HR=1.94, CI: 1.49-2.54) women with a latency <2 years (vs >10). Women with sBC after oropharynx carcinomas, lymphomas, leukemias, and prior BC consistently had worse survival than women with other primary tumors.

Conclusions: The survival of women who rapidly developed sBC, especially women whose primary cancer were breast, oropharyngeal or hematologic, had worse survival from their BC compared to those with a longer interval between the two cancers.

<<3>>   **EVALUATION AND IMPROVEMENT OF PREVIOUSLY REPORTED POLYGENIC RISK SCORES FOR BREAST CANCER IN PERUVIAN WOMEN**

Xiaosong Huang[1], Valentina A. Zavala[1], Sandro Casavilca-Zambrano[2], Jeannie Navarro-Vásquez[2], Carlos A. Castañeda[2], Guillermo Valencia[2], Zaida Morante[2], Monica Calderón[2], Julio E. Abugattas[2], Henry Gómez[2], Hugo A. Fuentes[2], Ruddy Liendo-Picoaga[2], Jose M Cotrina[2], Silvia P. Neciosup[2], Katia Roque[2], Jule Vásquez[2], Luis Mas[2], Marco Gálvez-Nino[2], Sixto E. Sánchez[3], Michelle A. Williams[4], Jovanny Zabaleta[5], Bizu Gelaye[4], Tatiana Vidaurre[2], Laura Fejerman[1,6]
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Background: Most of the genetic predisposition for breast cancer is explained by multiple common genetic variants of relatively small effect. A subset of these variants, which have been identified mostly in individuals of European and Asian ancestry, have been combined into a polygenic risk score (PRS) to predict breast cancer risk. We aimed to assess the performance of several previously published PRS sets with or without addition of Hispanic/Latino population specific single nucleotide polymorphisms (SNPs) in women of a relatively high proportion of Indigenous American (IA) ancestry from Peru.

Methods: Genome-wide genotype data were measured or imputed for 1,808 breast cancer cases and 3,334 controls sampled from Lima, Peru. Logistic regression was used to test the association between PRS and breast cancer risk. The Area Under the Curve (AUC) was used to estimate the prediction accuracy.

Results: We identified 3 PRS sets that have been previously studied in mostly European population. We added two SNPs discovered in Hispanic/Latino genome wide association studies to make additional sets. European PRS sets performed worse in the Peruvians than in Europeans. PRS sets with the two added Hispanic/Latino SNPs performed better. Analysis stratified by quartiles of IA ancestry showed better performance in the highest IA ancestry quartile compared to the lowest quartile. Analysis stratified by age at diagnosis showed that the European PRS sets performed similarly between age groups while the PRS sets with the added Hispanic/Latino specific SNPs performed better in the older age group.

Conclusion: Our result highlights the importance of developing ancestry-aware polygenic prediction models.

<<4>> FACTORS ASSOCIATED WITH EMERGENCY DEPARTMENT USE, TIMELINESS AND ACCESS OF HEALTH CARE IN OLDER ADULTS WITH LEUKEMIA AND LYMPHOMA

Alex J. Fauer, PhD, RN, OCN, Betty Irene Moore School of Nursing, UC Davis; UC Davis Comprehensive Cancer Center

Objective: Examine the association of ED use in the first year of diagnosis and patient experiences in care among older adults with hematologic malignancies.

Methods: Cross-sectional design using SEER-CAHPS® data from 2002 to 2015 to study Medicare fee-for-service enrollees with a primary diagnosis of leukemia or lymphoma. We linked the CAHPS survey data (patient-reported experiences with health services) to patients' cancer registry information and Medicare outpatient claims from the SEER-CAHPS resource. We estimated associations of ED use and clinical characteristics with two CAHPS outcomes – "getting care quickly" (timeliness) and "getting needed care" (access) – with bivariate and multivariate analyses.

Results: The analytic sample included 751 patients, 125 of whom had an ED claim in the first year of cancer diagnosis. The most frequent ED diagnosis clusters were fever and infection (n = 17, 13.6%), orthopedic and injury (16, 12.8%) and pain (16, 12.8%). Significantly more enrollees with an ED claim were diagnosed with lymphoma ($p < 0.01$), lived in rural areas ($p < 0.01$), and lived in areas with many families living in poverty ($p < 0.01$). In adjusted models, enrollees with an ED claim reported significantly worse access to care (β − 4.83; 95%CI -9.29,-0.38; $p = 0.03$).

Conclusions: The management of unplanned care concerns for adults with hematologic malignancies remains an important clinical and quality improvement imperative. Further study is warranted to enhance the management of emergent complications in older adults receiving care for hematologic malignancies, with efforts that enhance coordination of ambulatory oncology care.

<<5>> GUIDELINE-CONGRUENT CARE IS ASSOCIATED WITH INCREASED SURVIVAL AMONG ADOLESCENTS AND YOUNG ADULTS WITH PRIMARY MEDIASTINAL GERM CELL TUMORS: A POPULATION-BASE STUDY

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Background: Most prognostic factors and outcomes for primary mediastinal germ cell tumors (PMGCT) in adolescents and young adults (AYAs, 15–39) are obtained from single institutions or clinical trials with limited sample size. We aimed to assess, at the population-level, the impact of the delivery of guideline-congruent care (GCC), treating physician specialty, and location of care on survival among AYAs with PMGCT.

Methods: We used data from the California Cancer Registry (CCR) to ascertain AYAs diagnosed with PMGCT during 2004–2018, and to identify treatment information from the text-fields. GCC, defined based on the National Comprehensive Cancer Network and Children Oncology Group (COG) guidelines, includes chemotherapy alone (BEP: bleomycin, etoposide and cisplatin) or chemotherapy plus surgery. Multivariable Cox proportional regression was used for statistical analyses.

Results: Of 300 patients, 56% were of Hispanic race/ethnicity, 42% had late-stage disease (III/IV), 55% were treated by adult Hematologists/Oncologists, 27% received all their care at COG/NCI-designated cancer centers, and 50% received GCC. The most common histology type was seminoma (40%). AYAs with non-seminomas and late-stage disease were about 3-times more likely to die than those with seminoma tumors or earlier (I/II) stage (HR=3.14, CI 1.88–5.24 and HR=2.60, CI 1.72–3.93, respectively). GCC (versus non-GCC) was associated with improved survival (HR=0.66, CI 0.44–0.99). We found no differences in survival by physician specialty, location of care or sociodemographic factors.

Conclusions: GCC was independently associated with improved survival, underscoring the importance of following clinical practice guidelines when caring for the high-risk AYAs with PMGCT.

<<6>>   **LINKING THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH (CIBMTR) REGISTRY TO THE CALIFORNIA CANCER REGISTRY AND CALIFORNIA HOSPITAL PATIENT DISCHARGE DATA**

Ann Brunson[1], Julianne J.P. Cooley[2], Sara J. Schonfeld[3], Christa L. Meyer[4], Bryan Valcarcel[3], Renata Abrahao[1], Ted Wun[1], Jeffery Auletta[4,5], Lori Muffly[6], Lindsay M. Morton[3], Theresa H.M. Keegan[1]
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Advances in hematopoietic cell transplant (HCT) have substantially improved patient survival, increasing the importance of studying outcomes and long-term adverse effects in the rapidly growing population of HCT survivors. Large-scale registry data from the Center for International Blood and Marrow Transplant Research (CIBMTR) are a valuable resource for studying mortality and late effects after HCT, with detailed data reported by HCT centers on transplant-related factors and key outcomes.

To evaluate the robustness of CIBMTR outcome data and to assess health-related outcomes and healthcare utilization among HCT recipients, we linked data from the CIBMTR for California residents with the population-based California Cancer Registry (CCR) and hospitalization information from the California Patient Discharge Database (PDD).

In this retrospective cohort study, probabilistic and deterministic record linkage utilized key patient identifiers, such as social security number, zip code, sex, birth date, hematologic malignancy type and diagnosis date, and HCT type and date.

Among 22,733 patients in the CIBMTR who received autologous or allogeneic HCT for hematologic malignancy during 1991-2016, 89.0% were matched to the CCR and/or PDD. Unmatched patients were slightly more likely to have a first autologous (12.6%) than allogeneic (9.0%) HCT, a higher number of missing linkage identifiers, and to have received their HCT occurring prior to 2010. Among the patients reported to CIBMTR who matched to CCR, 85.7% demonstrated concordance of both hematologic malignancy type and diagnosis date across data sources. This linkage presents unparalleled opportunities to advance understanding of HCT practices and patient outcomes.

<<7>>   ACTIVATION OF NEURAL LINEAGE NETWORKS AND ARHGEF2 IN ENZALUTAMIDE-RESISTANT AND NEUROENDOCRINE PROSTATE CANCER CELLS AND ASSOCIATION WITH PATIENT OUTCOMES

Shu Ning[1], Jingge Zhao[1,2], Alan P Lombard[1], Leandro S D'Abronzo[1], Amy R Leslie[1], Masuda Sharifi[1], Wei Lou[1], Chengfei Liu[1,3], Joy C Yang[1], Christopher P Evans[1,3], Eva Corey[4], Hongwu Chen[3,5], Aiming Yu[3,5], Paramita M Ghosh[1,3,5,6], Allen C Gao[1,3,6]
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Background: Treatment emergent neuroendocrine prostate cancer (NEPC) after androgen receptor (AR) targeted therapies has been an aggressive variant of prostate cancer. Although various histology and biomarkers have emerged to characterize NEPC, the underlying mechanism for early neuroendocrine differentiation is poorly defined.

Methods: We performed transcriptomic analysis on the enzalutamide-resistant prostate cancer cell line C4-2B MDVR and NEPC patient databases to identify neural lineage signature (NLS) genes. Correlation of NLS genes with clinicopathologic features were determined. Cell viability was determined in C4-2B MDVR and H660 cells knocking down ARHGEF2 using siRNA. Organoids viability of patient-derived xenografts was measured after knocking down ARHGEF2.

Results: Here we show a NLS 95-genes representing the molecular landscape of neural precursor cell proliferation, embryonic stem cell pluripotency and neural stem cell differentiation, which may indicate an early or intermediate stage of neuroendocrine differentiation. These NLS genes positively correlate with conventional NE markers such as chromogranin and synaptophysin, and negatively correlate with AR and AR target genes. Differentially expressed NLS genes stratify NEPC from prostate adenocarcinoma, which are closely associated with clinicopathologic features such as Gleason Score and metastasis status. Higher ARGHEF2, LHX2, and EPHB2 levels correlate with a shortened survival time in NEPC patients. Furthermore, downregulating ARHGEF2 suppresses cell viability and markers of neuroendocrine in enzalutamide resistant and neuroendocrine cells.

Conclusions: The 95 neural lineage gene signature illustrates an early molecular alteration toward neuroendocrine differentiation, which could stratify advanced prostate cancer patients for better clinical treatment and serve as potential therapeutic targets in advanced prostate cancer.

<<8>>   CHARACTERIZATION OF INTERMEDIATE FILAMENT ASSEMBLIES THROUGH SOLID STATE NMR

Kayla M. Osumi, Dylan T. Murray, Department of Chemistry, University of California, Davis

Intermediate filaments (IFs) are cytoskeletal proteins known to play important roles maintaining cell structure and facilitating cell migration. IF's have long been used as a diagnostic marker for cancer, two examples include vimentin and GFAP which are known to be upregulated in certain cancers. Recent research has linked IF proteins to a more active role in cancer metastasis and invasion. Structurally, both follow typical IF construction, with a highly conserved alpha-helical rod domain and intrinsically disordered N-terminal head and C-terminal tail domain. Whilst the general self-assembly process of IF proteins is known, there is a lack of high-resolution structural information regarding filament structure. Differences in the head and tail domain structure of IFs lead to distinct localization and roles within cells. Understanding how variations in the intrinsically disordered domains of IFs impact function will require insight into filament structure and how these domains impact filament structure. This work aims to acquire high-resolution structural information on IF assemblies

through use of solid state NMR to understand how the differing intrinsically disordered head and tail domains affect IF structure . Due to a lack of well-established procedures for the study of IF networks by solid state NMR, current efforts have been toward optimizing the preparation of homogenous vimentin and GFAP filament assemblies for solid state NMR . This work will provide a basis for the study of other IF proteins through solid state NMR and contribute to a greater understanding of the roles IF proteins play in cancer progression.

<<9>> CHARACTERIZING CELLULAR TOPOGRAPHY AND MOLECULAR SIGNATURES OF IMMUNE CELL POPULATIONS IN THE CANINE BRAIN

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Naturally occurring canine glioma shares many features with human glioblastoma. Companion dogs may provide a distinct advantage over genetically and environmentally homogeneous laboratory mice for translational immunotherapeutic development, but a comprehensive analysis of the immune landscape in normal canine brain is needed. This proof-of-principle pilot aimed to define the distinct cellular populations of immune cells in healthy canine brain by single cell RNA sequencing (scRNA-seq). We utilized cryopreserved mononuclear cells from four brain regions of healthy, aged canine brain. Cells were stained and sorted via fluorescent-associated cell sorting to isolate putative microglia (CD11b+/CD45low/moderate), macrophages (CD11b+/CD45high), and lymphocytes (CD3high/CD11bneg), then combined and processed via 10X Genomics platform. Sequencing results were aligned to the canine reference genome, ROS_Cfam_1.0. Across brain regions, 2001.2+/-246.5 cells per sample were sequenced, with 159,652.8+/-16876.6 reads per cell, ultimately identifying 1354.7+/-29.0 genes per cell. Approximately 90% of genes were mapped to the reference genome. Gene signatures clustered into 6.6 +/-0.75 individual populations, with most clusters exhibiting up-regulation of genes associated with T and B lymphocytes (e.g., CD3, CD79A). Within each brain region, a single cluster of putative microglia were identified by strong expression of TMEM119, AIF1, and P2RY12. Top up-regulated genes within this cluster included C1QB, C1QC, CCL23, and APOE, suggesting activated, pro-inflammatory microglia. These data confirm that scRNA-seq is feasible on cryopreserved canine brain cells and demonstrates that there are distinct clusters of immune cells within the canine brain.

<<10>> CIRCADIAN CLOCK AND METABOLIC REGULATOR REV-ERBB CONTROLS ANDROGEN RECEPTOR SIGNALING IN PROSTATE CANCER

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Prostate cancer tumor growth and the disease progression are driven by the aberrant function of the androgen receptor (AR), thus making it a major therapeutic target for the disease treatment. However, resistance to prolonged anti-AR therapies is inevitable. Therefore, alternative treatments and/or new therapeutics are urgently needed for the advanced forms of the disease such as castration resistant prostate cancer (CRPC) and neuroendocrine prostate cancer (NEPC). Rev-Erbβ is a member of the nuclear receptor superfamily and functions typically as a transcriptional repressor to regulate circadian rhythm and lipid metabolism. Very few studies have focused on Rev-Erbβ function in cancer. Here we show that Rev-Erbβ knockdown strongly inhibits the growth of CRPC and NEPC cells. Rev-Erbβ overexpression promotes their survival. Our further studies including RNA-seq profiling showed that Rev-erbβ plays a major role in control of multiple gene programs including program of AR signaling, lipid metabolism, and neuroactive ligand signaling. Moreover, it also upregulates WNT signaling-related LRP6 and FZD3 protein expression. Therefore, our study provides the evidence that in models of advance prostate cancer, Rev-Erbβ plays a crucial role in control of gene programs conducive to the disease progression including the tumorigenic AR signaling. It also offers Rev-erbβ as a new therapeutic target for the advanced disease.

<<11>> DOES BURNING FAT MAKE TUMOR IMMUNE HOT? FAO ENHANCES TUMOR GROWTH WITH IMMUNE EVASION

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Metabolic reprogramming is a hallmark of cancer, however, it is unknown if cancer immune status can be changed by tumor metabolic rewiring under anti-cancer therapy. We have observed that mitochondrial energy output is dynamically adjusted to meet the increased cellular fuel demands for cell cycle progression and DNA damage repair. Such an adaptive metabolic rewiring is also required for timely boosting cellular energy output to fuel tumor radioresistance and metastasis. A metabolic shift from glycolysis-to-fatty acid oxidation (FAO) is observed in radioresistant breast cancer and glioblastoma cells and in animal tumors that are radiation treated but recur. Two major immune checkpoint (IC) proteins CD47 and PD-L1 which can protect the radioresistant tumor cells from immune clearance conducted respectively by macrophage phagocytosis and CD8+ T cells, are co-enhanced with enhanced mitochondrial FAO enzymes (CPT1A, CPT2 and ACAD9). Cancer patients with co-enhancement of the FAO enzymes and the ICs are associated with a poor prognosis. Such FAO controlled IC overexpression and immune evasion are identified with FAO derived cytoplasmic acetyl-CoA that upregulates the IC gene transcription via NF-κB/RelA acetylation. Inhibition of FAO by CPT1 inhibitor Etomoxir or CRISPR-mediated deletion of FAO enzyme CPT1A, CPT2, or ACAD9 re-sensitizes the radioresistant tumors to radiation with enhanced response to IC immunotherapy. These results suggest that radioresistant tumors promote FAO metabolism which not only provides cellular energy consumption for tumor growth but also causes tumor immune evasion via overexpression IC genes. Blocking FAO metabolism may raise tumor response to radiation combined immunotherapy.

<<12>> EN1 AS A POTENTIAL INDICATOR OF METASTATIC PROGRESSION IN PANCREATIC CANCER

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Pancreatic Cancer is one of the most lethal malignancies ranking as the 3rd leading cause of cancer related mortality with an average 5-year survival rate of less than 11%. Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent type accounting for 90% of all pancreatic cancer. Genetic alterations in KRAS and TP53 initiate the disease progression, driving the formation of pancreatic intraepithelial neoplasia (PanIN) and primary tumors. Then, epigenetic alterations, driven by transcription factors, promote PDAC progression and metastasis. Upregulation of EN1, a homeodomain transcription factor, correlates with poor patient survival. We hypothesize that certain clones within primary tumors acquire aberrant EN1 expression promoting PDAC metastasis. To test this hypothesis, we use a transgenic mouse model with an En1-EGFP allele to visualize En1 positive cells and cross with a PDAC mouse model, KPC mouse (Kras+/LSL-G12D; Trp53+/LSL-R172H; Pdx1-Cre) to get KPCG mouse (Kras+/LSL-G12D; Trp53+/LSL-R172H; Pdx1-Cre ;En1-EGFP). The genotypes of the mice will be confirmed through PCR and gel electrophoresis. Formalin-fixed paraffin-embedded tissues will be prepared, and GFP immunohistochemistry (IHC) will be performed to detect En1 positive cells. As expected, my preliminary GFP IHC data suggest that EN1 is expressed in a certain population of cells in brain, which requires a further validation for the specificity. We will determine when EN1 positive cells appear during PDAC progression and metastasis using KPCG mice. Our study will give us insights into the role of EN1 expression potentially contributing in development of improved treatment options for PDAC patients.

<<13>>   ENGRAILED-1 PROMOTES PANCREATIC CANCER PROGRESSION AND METASTASIS

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Pancreatic ductal adenocarcinoma (PDA) is one of the most challenging human malignancies, owing to its highly metastatic nature. While certain genetic mutations are known to drive PDA initiation and progression, a highly recurrent metastatic-specific mutation remains unknown. Instead, metastatic lesions harbor a similar genetic mutation profile as seen throughout the primary tumor, suggesting fluctuations in gene expressions among primary tumor are critical for acquiring the metastatic traits. Here, we report a developmental transcription factor homeobox protein Engrailed-1 (EN1) as a pro-survival factor in murine metastatic PDA and hypothesize that EN1-mediated transcriptional and epigenetic changes accelerate PDA progression and metastasis. Using the next-generation sequencing approaches, we identified the direct EN1 targets, which functionally repress cell death pathways and promote proliferation and migration. Phenotypically, EN1 expressions in murine PDA positively contribute to the aggressive characters both in vitro and in vivo. Furthermore, using both publicly available transcriptomic profiles and tissue microarrays of PDA patients, we found EN1 expression is an independent prognostic factor for patient poor prognosis. With the goal to improve PDA patient survival outcomes and to mitigate the disease progression, we showed EN1 plays a critical role in promoting PDA metastasis, which potentially offers an avenue to improve the current chemotherapeutic responses and/or the development of new treatment strategies.

<<14>>   EPIGENETIC REGULATOR HISTONE METHYLTRANSFERASE G9A DRIVES NEPC PROGRESSION THROUGH PROMOTING NEURONAL LINEAGE DIFFERENTIATION

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Neuroendocrine prostate cancer (NEPC) is a highly aggressive, lethal form of prostate cancer with a short survival time (typically < 12 months) from detection, arising either de novo or from primary adenocarcinoma (PRAD) treated with anti-androgen receptor (AR) signaling therapies. Neuronal lineage differentiation is now recognized as a major mechanism that confers resistance to most of the current therapies. The exact molecular events accompanying the aberrant lineage differentiation and their plasticity remain poorly defined. Epigenetic alterations in the tumors have been strongly implicated. However, so far only a few drivers and therapeutic targets of NEPC diseases have been examined. Here we identified histone methyltransferase G9a as a strong candidate of therapeutic target in NEPC. G9a is overexpressed in NEPC tumors and associated with poor clinical outcomes. Knockdown and CRISPR knockout of G9a significantly repressed cell proliferation and expression of putative NEPC drivers and markers. Inhibitors of G9a displayed strong activities in suppression of growth and survival of NEPC cells and PDX organoids. Among them, CM272, a new first-in-class, reversible G9a/DNMT1 dual inhibitor, showed the highest potency. Furthermore, G9a antagonists displayed strong activities in inhibition of the growth of PDX tumors. Our RNA-seq gene expression profiling demonstrated that among gene programs downregulated by the treatments, neuron differentiation and axonogenesis are significantly enriched. Our G9a ChIP-seq data indicated that G9a directly controls the expression of genes involved in neuronal lineage differentiation program and that G9a inhibitor diminishes its occupancy at the gene regulatory sites. Therefore, our study revealed that epigenetic regulator G9a is a key driver of NEPC and identified a new strategy for treatment of NEPC by targeting G9a.

<<15>>   INHIBITION OF PHOSPHOLIPASE D1 REDUCES PANCREATIC CARCINOGENESIS IN MICE

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Pancreatic ductal adenocarcinoma (PDA) is a leading cause of cancer-related death in the United States. Phospholipase D1 (PLD1) is a lipid-signaling enzyme that plays a role in signaling pathways regulating cell proliferation and survival/apoptosis. PLD1 activity has been shown to promote tumor progression in other cancer types, however, its role and mechanisms in pancreatic cancer is not yet understood. The objective of this study is to determine the role of PLD1 regulation in pancreatic carcinogenesis through genetic-ablation and pharmacological inhibition of PLD1. Cohorts of male and female LSL-KrasG12D/+;Ptf1Cre/+ (KC) mice and KC with PLD1 knockout (KC; Pld1-/-) mice were euthanized at 8 months old and the pancreas examined. At 8 months of age, there was a significant difference ($p<0.05$) in the pancreas weight at sacrifice between the KC mice and the KC; Pld1-/- mice. This was due, in part, by a reduction in tumor proliferation. To assess whether pharmacological inhibition of PLD could prevent pancreatic carcinogenesis in KC mice, cohorts of 9-12 male 7-month-old KC mice received daily intraperitoneal injections of a small molecule inhibitor of PLD (FIPI) at a dosage of 3 mg/kg of body weight for a duration of 5 weeks. At 8.5 months of age, histological analysis indicated that FIPI-treated KC mice displayed less acinar cell loss compared to vehicle-treated KC controls. Moreover, treatment with FIPI significantly reduced cell proliferation ($p<0.01$) in KC mice in comparison to vehicle-treated KC mice. In summary, these results indicate that PLD1 plays a critical role in pancreatic carcinogenesis and may represent a novel therapeutic target.

<<16>>   METABOLISM-MASTER REGULATOR SREBP2 REACTIVATES DEVELOPMENTAL PROGRAM IN TRIPLE-NEGATIVE BREAST CANCER

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Reactivation of specific developmental programs is strongly implicated in cancer progression. Wnt signaling is one of the key cascades regulating in development and stemness. Aberrant Wnt/β-catenin signaling pathway facilitates cancer stem cell renewal, cell proliferation and differentiation, thus exerting crucial roles in tumorigenesis and therapy resistance. Triple-negative breast cancer (TNBC) displays poor tumor cell differentiation, high metastasis and recurrence rate, and high tendency to develop chemoresistance. Wnt signaling plays an major role in TNBC. Agents targeting Wnt/β-catenin signaling has therapeutic potential in preclinical studies and clinical trials. Deregulated lipid and cholesterol homeostasis are often associated with tumorigenesis and cancer progression. Sterol regulatory element binding protein-2 (SREBP-2) is master regulator of cholesterol homeostasis. Here, we report that gene knockdown or pharmacological inhibition of SREBP2 suppressed the cholesterol biosynthesis program. Unexpectedly, we also found that inhibition of SREBP2 markedly inhibited activation of Wnt signaling and pathways regulating pluripotency of stem cells, which were corroborated by results from protein expression analysis and tumor sphere formation. Our further studies demonstrated that SREBP2 and β-catenin interacts with each other, and that their association can be disrupted by SREBP2 inhibition. Our ChIP-seq analysis revealed that SREBP2 and β-catenin co-occupies at WNT signaling and pluripotency of stem cell program genes and co-regulates their expression. Our work reveals an unexpected function of metabolism-master regulator SREBP2 in reactivation of key developmental programs and suggests a new therapeutic strategy for treatment of advanced TNBC.

<<17>>   MOLECULAR AND HISTOLOGICAL CHARACTERIZATION OF TWO GENETICALLY ENGINEERED MOUSE MODELS OF NON-SMALL CELL LUNG CANCER

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Non-small cell lung cancer (NSCLC) patients typically display little to no symptoms until late-stage disease, resulting in ~80% of patients being diagnosed at advanced stages when response to therapy is low. Effective pre-clinical models are needed to accurately reflect NSCLC disease progression and improve basic NSCLC research. This work characterizes two genetically engineered mouse models (GEMM) that reflect human NSCLC. These mouse lines utilize a cre recombinase system to induce the expression of two oncogenic mutations (Kras, Tp53) in club cells or alveolar epithelial cells based on cell type-specific promoters (Scgb1a1, Sftpc), thereby inducing NSCLC in mice. Furthermore, these mice harbor transgenes specific for cancer tracking (GFP, Metrs). Cancer mutations were induced at 6-weeks of age and lung samples were collected for molecular (single-cell RNA sequencing) and histological (H&E scoring) analysis throughout disease progression. Molecular analysis revealed the club cell model had more B cells and macrophages than the alveolar cell model at the early timepoint. The alveolar cell model showed an increase in type 2 epithelial cells and a decrease in immune cells over time. Histological scoring of the club cell model at early timepoints showed many hyperplasias which developed into invasive carcinomas in the bronchioles and alveoli, while the alveolar cell model progressed rapidly and exhibited adenocarcinomas and squamous cell carcinomas. These findings suggest that the GEMM models accurately represent human NSCLC due to their cellular profile, morphology, and localization within the lung. These models have the potential to identify biomarkers of NSCLC progression to improve patient prognosis.

<<18>>   TARGETING METABOLIC ADDICTION AND DNA REPAIR OF THERAPY-RESISTANT PROSTATE CANCER

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Background: Arginine is an indispensable amino acid for the synthesis of proteins, nucleotides, polymethines, nitric oxide etc. In normal cells, arginine is "non-essential", since it can be synthesized de novo from citrulline via argininosuccinate synthase1 (ASS1), and argininesuccinate liase (ASL). ASS1 is the rate-limiting enzyme in the pathway converting aspartate to fumarate. However, in prostate cancer (PCa), ASS1 expression is suppressed due primarily to promoter methylation, hence, intrinsic arginine production is blocked. Therefore, extrinsic (dietary) arginine becomes critical to the survival of PCa cells. Arg also inhibits AMP-activated protein kinase (AMPK), as illustrated by the activation of AMPK and suppression of mTOR phosphorylation by ADI-PEG20. A major function of AMPK is regulation of the mitochondrial ETC complex; and metformin is known to regulate mitochondrial functions. In this project, we investigate the role of the androgen receptor (AR) in ASS1 function.

Methods: Formalin fixed paraffin embedded (FFPE) tissues and clinical data of 78 patients who underwent radical retropubic prostatectomy at VA Northern California Health Care System (VANCHCS) between 1999 and 2004 were extracted from the VANCHCS archives. In another set, 51 metastatic lesions from patients who were diagnosed with metastatic PCa (mPCa) between 1995 and 2013 were obtained from the archives of Mayo Clinic, Rochester, MN. Balb/c mice were left intact or castrated, with or without testosterone supplement

(n=6/arm). We used androgen sensitive LNCaP and its CRPC derivative C4-2B, AR-null PC-3 and DU-145, 22Rv1 cells expressing AR splice variants lacking the ligand-binding domain (LBD) and AR positive and androgen sensitive VCaP cells that were derived from a CRPC patient. Cells were cultured in RPMI media containing fetl bovine serum (FBS) containing hormones and growth factors or in charcoal stripped serum (CSS) lacking these factors. Alternatively, cells were cultured in media lacking arginine in the presence or absence of metformin. Pegylated arginine deiminase (ADI-PEG20) was used for arginine depletion.

Results: We observed a significant decrease in ASS1 in localized PCa compared to non-tumor prostate (p=0.0079); within the PCa tissues, ASS1 levels decreased with an increase in Gleason scores (p=0.006). ASS1 levels negatively correlated with the proliferation marker Ki67 (p=0.015). Examination of mPCa tissues showed higher overall survival (OS) in ASS1-positive patients. Significantly, AR and PSA levels negatively correlated with ASS1 in mPCa. Castration of mice increased ASS1 levels in the prostate, while testosterone reversed this effect. However, testosterone in intact mice also increased ASS1 levels. LNCaP and C4-2B express high ASS1; in contrast, PC-3, DU-145, 22Rv1 and VCaP cells lack ASS1 expression. Culture of LNCaP cells in CSS translocated ASS1 from the nucleus to the cytoplasm, whereas in CRPC lines, ASS1 was exclusively cytoplasmic. In contrast to AR-positive PCa, transfection of AR into AR-null PC-3 cells upregulated ASS1 levels. In AR-positive C4-2B, chemoresistance elevated ASS1 while in AR-null DU-145 cells, chemoresistance inhibited it. Thus, chemoresistant C4-2B cells were not sensitive to ADI-PEG20, whereas chemoresistant DU-145 cells were. Simultaneous knockdown of AR and ASS1, but not that of ASS1 alone, increased sensitivity to ADI-PEG20. AR- and ASS1-negative TRAMP cells were highly susceptible to ADI-PEG20. Negative correlation between AR and ASS1 was observed in AR expressing cells whereas in AR-null cells, a positive correlation was observed. AR- and ASS1-null PC-3 and TRAMP cells, bit not AR-positive LNCaP and C4-2B, showed a synergistic effect of ADI-PEG20 and metformin. In AR-positive but ASS1-null 22Rv1 cells, metformin failed to accelerate the effects of ADI-PEG20. Investigation of the mechanism of ADI-PEG20 and metformin synergism revealed a role for Akt phosphorylation. Metformin increased the phosphorylation of Ataxia-telangiectasia mutated (ATM) kinase, that regulates DNA damage repair, in the presence of arginine, but not in arginine depleted media. Metformin also suppressed the phosphorylation of DNA-PK but increased the phosphorylation of γH2AX and HSP90 in arginine free medium. The amino acid deficiency sensor GCN2 is increased upon arginine deprivation, but metformin prevented this effect; however, it had no effect on AR expression.

Conclusions: These results indicate that arginine deprivation is an effective means of PCa inhibition only in AR-null cells, whereas metformin sensitizes PCa cells to arginine deprivation by suppressing DNA damage repair.

<<19>> GIGAFIBI; RAPID, LARGE-FORMAT HISTOLOGY-RESOLUTION IMAGING FOR INTRAOPERATIVE ASSESSMENT OF BREAST LUMPECTOMY MARGINS

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More than 280,000 women in the United States are diagnosed with breast cancer each year. The majority of these women qualify for breast conserving surgery (BCS), which is also known as a lumpectomy or partial mastectomy. Despite advances in preoperative imaging, the positive surgical margin rate remains significant, with residual tumor present in 5-40% in published reports. The current standard of care for pathology examination of lumpectomy provides only post-procedural guidance which results in re-excision of the surgical margins in search of residual carcinoma at a substantial cost both in terms of anxiety and morbidity associated with additional surgery, as well as the actual costs to the health care system.

We have developed FIBI (Fluorescence Imitating Brightfield Imaging), a technology which produce digital images from fresh tissue, within minutes that closely, resemble standard histology. Based on our FIBI technology, we plan to develop GigaFIBI, a novel histology-grade imaging approach for margin evaluation of fresh breast lumpectomy specimens providing surgical guidance in an intraoperative setting. Diagnostic-quality microscopic images using GigaFIBI methodology obtained from large (up to 100 x 100 mm2) tissue surfaces can be available within 7 minutes of fresh tissue grossing.

GigaFIBI can provide sensitive and specific lumpectomy margin assessment feasible for intraoperative surgical guidance. This has potential to dramatically reduce the rates of final positive margins requiring additional surgery, with the accompanying morbidity, psychosocial risk, and personal/health care system costs.

<<20>> MODIFICATION OF HYALURONIC ACID FOR CD44 AND INTEGRIN AVB6 DUAL TARGETING AND RADIO-LABELING

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Introduction: Among promising targets for cancer therapy is CD44, which hyaluronic acid (HA) binds but with a low affinity. This can be improved by adding another tumor-targeting ligand. Here, we synthesized dual targeting agents by combining HA with αvβ6-BindingPeptide (αvβ6-BP, targeting the cancer-associated integrin αvβ6) to target both CD44 and αvβ6, and explored the feasibility of radiolabeling these agents for positron emission tomography imaging.

Methods: HA (10-200 kDa) was modified with either DOTA chelators, or αvβ6-BP-DOTA conjugates, and radiolabeled with copper-64. The radiolabeled agents were evaluated in vitro for cell binding and internalization.

Results: The formation of HA-DOTA and HA-[αvβ6-BP-DOTA] was confirmed by UV spectrophotometric analysis. For all the HA constructs tested, the incorporation of copper-64 was ≥85%. [64Cu]Cu-[HA-DOTA] showed low binding (<12%) and internalization (<3%) to DX3puroβ6 (CD44+αvβ6+) and DX3puro (CD44+αvβ6-) cells, and no selectivity for αvβ6 (DX3puroβ6/DX3puro ratio <1.1). Conversely, [64Cu]Cu-[HA-[αvβ6-BP-DOTA]] showed a high binding (58 - 66%) and internalization (48 -51% of total radioactivity) to the DX3puroβ6 cells. The selectivity for αvβ6 increased with increasing molecular weight of HA.

Conclusion: Hyaluronic acid was successfully modified to yield dual targeting (CD44 and αvβ6) agents by conjugating αvβ6-BP-DOTA onto HA. The resulting agents were successfully radiolabeled with copper-64. The αvβ6-targeted [64Cu]Cu-[HA-[αvβ6-BP-DOTA]] demonstrated significantly higher binding to and internalization into αvβ6+ cells, as compared to the non-αvβ6-targeted analogs. The selectivity for αvβ6 increased with increasing MW of HA. Given the promising in vitro data obtained for [64Cu]Cu-[HA-[αvβ6-BP-DOTA]], further investigation into their potential as in vivo PET imaging agents is warranted.

<<21>> A PH-DRIVEN SMALL-MOLECULE NANOTRANSFORMER HIJACKS LYSOSOMES AND OVERCOMES AUTOPHAGY-INDUCED RESISTANCE IN CANCER

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Smart conversion of supramolecular structures in vivo is an attractive strategy in cancer nanomedicine, which is usually achieved via specific peptide sequences. Here we developed a lysosomal targeting small-molecule

conjugate, PBC, which self-assembles into nanoparticles at physiological pH and smartly converts to nanofibrils in lysosomes of tumor cells. Such a transformation mechanically leads to lysosomal dysfunction, autophagy inhibition, and unusual cytoplasmic vacuolation, thus granting PBC a unique anticancer activity as a monotherapy. Importantly, the photoactivated PBC elicits significant phototoxicity to lysosomes and shows enormous advantages in overcoming autophagy-caused treatment resistance frequently occurring in conventional phototherapy. This improved phototherapy achieves a complete cure of oral cancer xenografts upon limited administration. Our work provides a new paradigm for the construction of nonpeptide nanotransformers with biomedical activities. Efforts have been devoted to expanding the applications of this innovative nanoplatform in different cancer types and translating it into clinical trials.

<<22>> AN EXCEPTIONAL TUMOR RESPONSE TO NOVEL CTLA-4 INHIBITOR ONC-392 IN A PATIENT WITH REFRACTORY ADENOID CYSTIC CARCINOMA: A CASE REPORT FROM AN ONGOING CLINICAL TRIAL

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Adenoid cystic carcinoma (ACC) is a rare type of cancer that primarily originates from salivary glands but also from a variety of other organs. While local therapy with surgery and/or radiation are the primary treatment modalities, no systemic therapy has been approved by the FDA for patients with refractory or metastatic ACC. Here, we report a 49-year-old woman with refractory, aggressively growing ACC who had an exceptional tumor response to a novel CTLA-4 inhibitor, ONC-392. She was diagnosed with cT3N0M0 ACC of the left nasal cavity on 2/21/2018 and received definitive radiation, completed on 2/4/2019. She had 2 salvage surgeries for local recurrences on 1/15/2020 and 4/23/21, and received re-irradiation with concurrent cisplatin, completed on 7/21/2021. On 10/19/2021, she was found to have a biopsy-proven recurrent tumor and lung metastasis. She started ONC-392 on 1/6/2022, and while the tumor mass grew from 7.7 x 4.1 cm to 10.0 x 8.0 cm after 2 cycles of treatment, a confirmatory MRI scan after 3 cycles showed a >80% tumor reduction. Currently, the patient has received 9 cycles of treatment and remains in good tumor response without any significant toxicity. Tumor biomarker studies identified both a MYB-NFIB gene rearrangement and NOTCH1-activating mutations that are associated with aggressive ACC. Ongoing correlative studies aim to uncover the underlying mechanisms behind this exceptional tumor response to ONC-392. Based on this case, a phase II study of ONC-392 monotherapy is accruing patients with refractory or metastatic ACC of different tumor origins.

<<23>> AN INTEGRATED MULTIDISCIPLINARY EVALUATION PLATFORM AND EARLY EXPERIENCE FOR PRECISION THERAPY IN RESECTABLE NSCLC

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Biomarker-guided neoadjuvant therapies can improve pathological outcomes, reduce systemic recurrences, and improve cure rates in patients with resectable NSCLC. However, this requires a paradigm shift in clinical practice. The objective of this study was to establish a multidisciplinary clinical workflow for identifying early-stage NSCLC patients for precision neoadjuvant therapy and summarize our early experience. Retrospective review of 17 NSCLC patients who were screened for neoadjuvant therapy showed that 11 (65%) of patients received the planned neoadjuvant systemic treatment and surgery. The barriers for successful neoadjuvant therapy included patient preference for prompt surgery (N=3), tumor progression (N=2), and unresectable tumor (N=1). We have developed an integrated multidisciplinary clinical workflow for expediting molecular and immune biomarker testing and identifying appropriate patients for precision neoadjuvant therapy. The LCMC4 (LEADER) trial screens for the following oncogenic drivers: mutations in EGFR, BRAFV600E, MET exon 14, KRAS G12C, and HER2, rearrangements in ALK, RET, NTRK, and ROS1, and amplification of MET and HER2. Using this platform, we have screened 11 patients in the neoadjuvant biomarker screening trial over the past 2 months. Two patients had actionable targets that could be matched to neoadjuvant/adjuvant targeted therapy trials. For those patients who do not have actionable molecular targets, we are developing a clinical trial to prospectively evaluate the efficacy of new standard of care neoadjuvant chemoimmunotherapy in patients with different racial ethnicities (Asian, Latino/Hispanic, and Black/African American patients, compared to non-Hispanic White patients). The co-primary endpoints are surgical resection rate and pathological response (pCR and MPR).

<<24>> AN INTEGRIN AVB6 BINDING PEPTIDE-DRUG-CONJUGATE FOR TUMOR TARGETED DRUG DELIVERY

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Cancer therapies exhibit high systemic off-target toxicities that can be reduced by combining a tumor-targeting moiety with the therapeutic agent. Integrin αvβ6 is a cell surface receptor that is highly expressed on many cancers and is selectively targeted by the αvβ6 Binding Peptide (αvβ6 -BP), developed in our lab and used to image metastatic disease. The goal of this study was to develop a peptide drug conjugate, [64Cu]PDC-1 (Fig. A), for tumor targeted drug delivery by combining αvβ6 -BP and monomethyl auristatin E (MMAE) via a cathepsin cleavable linker that was radiolabeled with copper-64 for PET imaging. [64Cu]PDC-1 showed alphavbeta6-dependent cytotoxicity by WST-1 assay (EC50: DX3puroβ6 (+) 0.058±0.003 nM, DX3puro (-) >5 nM; MMAE, EC50 ≤0.5 nM to both cell lines) and αvβ6-dependent cell binding [DX3puroβ6 (+) 67.0±2.3%, BxPC-3 (+) 62.0±1.0%; DX3puro (-) 4.4±0.1%]. [64Cu]PDC-1 showed >98% stability in human serum at 37˚C. In vivo PET/CT & biodistribution showed αvβ6-selective tumor accumulation [% ID/g, 4 h: DX3puroβ6 (+) 4.46±0.91; BxPC-3 (+) 4.61±1.44; DX3puro (-) 0.56±0.12; Fig. B & C]. Therapeutic efficacy of [NatCu]PDC-1 was measured against controls of saline, [NatCu]-C-αvβ6-BP, and MMAE in mice bearing xenograft tumors [DX3puroβ6 (+) or DX3puro (-)]; it showed prolonged αvβ6-dependent survival [median survival; DX3puroβ6 (+) treated - 77 days; DX3puro (-) treated - 49 days; all controls - 37 days, Fig. D). Combining the cytotoxic MMAE with the αvβ6-BP in [64Cu]PDC-1 resulted in αvβ6-dependent cytotoxicity, cell binding, internalization, and αvβ6-targeted tumor uptake. Furthermore, [64Cu]PDC-1 displayed promising in vivo therapeutic efficacy, warranting future evaluation.

<<25>> ARID1A ALTERATIONS AS POSITIVE PREDICTORS OF IMMUNE CHECKPOINT INHIBITOR EFFICACY IN ADVANCED NON-SMALL CELL LUNG CANCER: REAL WORLD DATA ANALYSIS

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Introduction: Loss of function (LOF) alterations in ARID1A are recurrent in cancer and may predict better outcomes with immune checkpoint inhibitor (ICPi) therapy. Here we present real-world data (RWD) from patients with advanced non-small cell lung cancer (NSCLC) tested via a commercially available circulating tumor DNA (ctDNA) assay to assess the impact of LOF ARID1A alterations on ICPi efficacy.

Methods: Patients with NSCLC who: (a) received pembrolizumab (pembro) +/- chemotherapy as part of a 1st-line regimen after 1/1/2020, (b) underwent ctDNA testing prior to treatment initiation, and (c) had detectable ctDNA, were identified via the Guardant INFORM database. LOF ARID1A alterations were defined as frameshift, nonsense or canonical splice site alterations, and were further categorized as clonal (copy number-adjusted mutation allelic fraction/maximum somatic mutation allelic fraction >50%) or subclonal (< 50%). Time to treatment discontinuation (TTD) and time to next treatment (TTNT) were compared using a one-sided pairwise log-rank test.

Results: In total, 2,186 patients were eligible. Of these, 122 (5.6%) had LOF ARID1A, with 60 (49%) harboring ≥1 clonal ARID1A alteration. Clonal LOF ARID1A alterations were significantly associated with improved TTNT versus patients without LOF ARID1A.

Conclusion: Overall TTNT and one-year next-treatment-free survival were significantly longer in patients with clonal LOF ARID1A alterations versus those without. This RWD further supports the potential utility of ARID1A alts as a positive predictive biomarker of ICPi benefit.

<<26>> ASSESSING SYSTEMIC AND LOCAL LEVELS OF LIDOCAINE DURING SURGERY FOR GLIOBLASTOMA

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Background: Glioblastoma is the most common primary brain tumor and is incurable. Median survival is 15 months. Studies in vitro and in humans have suggested that lidocaine may have anti-neoplastic properties in glioblastoma. The pharmacokinetics of lidocaine penetration into glioblastoma have not been studied.

Objective: The primary objective of this study is to characterize the pharmacokinetics of lidocaine penetration into glioblastoma during tumor resection. The secondary objective is to assess the progression free survival (PFS) and overall survival (OS) of these patients.

Method: The study group received a bolus of 1.5mg lidocaine/kg ideal body weight (IBW) followed by a 2.0 mg lidocaine/kg IBW/hr infusion. Up to 3 tumor samples and peripheral blood samples were collected hourly during resection of glioblastoma. Patients were intended to receive the Stupp protocol. Patients were followed for adverse events, median PFS and OS. The concentration of lidocaine in the tumor tissue and peripheral blood will be determined with mass spectroscopy.

Results: Twelve patients with IDH wild-type glioblastoma were included in this study. At most recent follow-up, PFS is 7.8 (95% CI 3.4-12.1) months and OS is 9.5 (95% CI 5.4-13.5) months. Seven (58.3%) patients have

died. Two patients had serious adverse events, including headache, hypoxia and intraoperative infarct and hemorrhage.

Conclusion: Lidocaine combined with intention to treat with standard of care resulted in a PFS of 7.8 months and OS of 9.5 months in patients with glioblastoma with challenging molecular characteristics. Method development is underway for measuring lidocaine concentration in glioblastoma samples with mass spectroscopy.

<<27>>   BIOENGINEERING NOVEL SIRNA AGENTS FOR CANCER RESEARCH VIA IN VIVO FERMENTATION

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Upcoming research shows that RNA based drugs have the capability to approach targets that are otherwise 'undruggable' by other alternatives such as small molecules and proteins, thus opening up a whole new direction for treating incurable diseases. Among the RNA based drugs are RNAi agents (e.g., miRNAs and siRNAs) that can inhibit target gene expression via intercepting related messenger RNA. One major challenge lies in that the current RNAi research and development is limited to the use of chemically synthesized RNAi agents carrying extensive and various artificial modifications for stability which, however, may induce immunogenicity. In this study, we aimed to optimize the tRNA/pre-miRNA-based technology to achieve in vivo fermentation production of fully humanized biologic siRNA agents (Bio-siRNA). We first achieved high-level heterogenous overexpression (accounting for >50% of total bacterial RNA) of 10 target Bio-siRNA molecules at 100% success rate, yielding 10-40 mg Bio-siRNA per liter bacterial culture with high-purity (≥98.5%) and low endotoxin (<1.5 EU/µg RNA). Further studies demonstrated that target siRNAs (e.g., PDL1-siRNA) are specifically released from PDL1-Bio-siRNA in human NSCLC cells to downregulate specifically protein levels of targeted genes to about 70-80%. Also, GFP-Bio-siRNA was effective in knocking down GFP fluorescent intensity in multiple cell lines tested at different time points after transfection. This robust RNA bioengineering platform offers a novel class of true biologic siRNA agents, which are produced and folded in living cells, for basic research and experimental therapies.

<<28>>   CHARACTERIZATION OF NATURAL KILLER AND CYTOTOXIC T CELL IMMUNE INFILTRATES IN OSTEOSARCOMAS

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Background: Osteosarcoma (OSA) is an aggressive cancer characterized by a poor prognosis. The tumor immune microenvironment has been poorly described. Our objective was to evaluate OSA immune parameters, including natural killer (NK) cells, to determine if NK cells associate with outcomes.

Methods: We analyzed tumors from 16 OSA patients treated from 1998 – 2014. Predictor variables included tumor infiltrating lymphocytes (TILs), T cell markers (CD3+, CD8+, CD45RO+), NK markers (NKp46) and NK inhibitory markers (TIGIT and MHC-I). TILs were scored from 0-3, and immune markers were scored from 0-300. Primary outcome variables were progression-free survival (PFS) and overall survival (OS), analyzed by the Kaplan-Meier method.

Results: Mean age was 20, 62% were male, and the mean tumor size was 9.8±2.5cm. All patients received neoadjuvant chemotherapy. Median survival was 151 months and median progression-free survival was 36 months. Immune expression scores were low at biopsy, and there was no significant change at resection following chemotherapy. There was no association of TILs, NK cells, or T-cell subsets with survival outcomes.

CD8+ T cells were the most prevalent immune subset. The proportion increased post chemotherapy but was not statistically significant. MHC-I mean expression score decreased from 15.3±14 to 2.3±5.3 (p=0.008) following therapy, but changes did not predict survival.

Conclusion: NK and T cell infiltrates are overall low in OSA and do not associate with oncologic outcomes. Further characterization of the immune infiltrate in OSA, including inhibitory signals and suppressive cell types, may yield better biomarkers of prognosis and immune targeting in this refractory disease.

<<29>> HIGH LABYRINTHIN EXPRESSION IS ASSOCIATED WITH POOR PROGNOSIS IN PATIENTS WITH NSCLC

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Background: Labyrinthin (Laby) is a novel tumor-specific protein expressed on the cell surface of most adenocarcinomas of various cancer types. This study aimed to develop immunohistochemistry (IHC) assay to detect Laby expression on archival tumor specimens and characterize the clinical significance of Laby expression.

Methods: Tissue microarrays (TMAs) were prepared from archival tissue blocks containing 161 NSCLC patients, which included 91 adenocarcinoma (LUAD), 46 squamous carcinomas (LUSC), and 24 other histology types. Using a newly developed IHC assay, TMA sections were stained and scored for Laby expression by percentage of tumor cell expression as negative (0 5%) or positive (>5%). Kaplan-Meier curves and log-rank tests were used to compare overall survival between IHC score groups.

Results: Laby IHC expression (>5%) was detected in 125/161 (77.6%) of NSCLC samples and was associated with poor overall survival (HR = 3.6, 95% CI: 2.3-5.4; p <0.0001) compared with those patients with negative Laby expression. Multivariate survival analysis demonstrated that Laby expression was an independent prognostic factor for NSCLC patients (HR = 2.01, 95% CI: 1.04-3.9; p=0.038). There was also a significant correlation between Laby expression and metastasis, male gender and white race, but no correlation with smoking history, COPD history, and histological type. The study to characterize Laby expression in human cancers using the TCGA database is still ongoing.

Conclusion: Laby IHC expression was associated with poor prognosis in NSCLC patients. This assay is being used to identify candidate cancer patients for the first-inhuman phase I trial evaluating the Laby vaccines (UCDCC#296, NCT051013560).

<<30>> HUMAN SOFT TISSUE SARCOMAS HARBOR AN INTRATUMORAL VIRAL MICROBIOME WHICH IS LINKED WITH NATURAL KILLER CELL INFILTRATE AND PROGNOSIS

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Background: Groundbreaking studies have linked the gut microbiome with immune homeostasis and anti-tumor immune responses. Mounting evidence has also demonstrated an intratumoral microbiome, including in soft tissue sarcomas (STS), although detailed characterization of the STS intratumoral microbiome is limited. We sought to characterize the intratumoral and gut microbiome in STS patients undergoing preoperative radiotherapy (RT) and surgery, hypothesizing the presence of a distinct intratumoral microbiome with potentially clinically significant microbial signatures.

Methods: We prospectively obtained tumor and stool samples from adult patients with non-metastatic STS using a strict sterile collection protocol to minimize contamination. Metagenomic classification was used to estimate abundance using genus and species taxonomic levels across all classified organisms, and data were analyzed with respect to clinicopathologic factors.

Results: Fifteen patients were enrolled. Most tumors were located at an extremity (67%) and were histologic grade 3 (87%). 40% were well-differentiated/dedifferentiated liposarcoma histology. With a median follow up of 24 months, four (27%) patients developed metastases, and three (20%) died. Despite overwhelming human DNA (>99%) intratumorally, we detected a small but consistent proportion of bacterial DNA (0.02-0.03%) in all tumors, including Proteobacteria, Bacteroidetes, and Firmicutes. In patients that developed metastases, Piscirickettsia (P=0.002) and Respirovirus (P=0.04) were differentially relative abundant genera in the pre-RT tumor microbiome. In the tumor microenvironment, we observed a strong positive correlation between viral relative abundance and natural killer (NK) infiltration, and there was a clear trend for higher NK infiltration to associate with superior metastasis-free and overall survival by immunohistochemical, flow cytometry, and multiplex immunofluorescence analyses.

Conclusions: We prospectively demonstrate the presence of a distinct and measurable intratumoral microbiome in STS patients at multiple time points. Our data suggest that the STS tumor microbiome has prognostic significance with viral relative abundance associated with NK infiltration and oncologic outcome. Additional studies are warranted to further assess the clinical impact of these findings.

<<31>>   IGFBP3 PROMOTES RESISTANCE TO OLAPARIB VIA MODULATING EGFR SIGNALING IN ADVANCED PROSTATE CANCER

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Castration-resistant prostate cancer (CRPC) remains an incurable disease and a leading cause of cancer death in men. Olaparib was among the first PARP inhibitors (PARPi) approved for the treatment of CRPC tumors harboring DNA repair defects. However, resistance to PARPi's has been documented. The mechanisms underlying resistance to PARPi's remain elusive. To study resistance, we developed olaparib-resistant LN-OlapR and 2B-OlapR cell lines through chronic olaparib treatment of the olaparib-sensitive cell lines LNCaP and C4-2B, respectively. RNA-seq revealed IGFBP3 is overexpressed in both OlapR cell lines. IGFBP3 overexpression is correlated with poor clinical outcome and is thought to participate in DNA repair pathways via nonhomologous end joining through a ternary complex with the epidermal growth factor receptor (EGFR) and DNA-PKcs. We hypothesize that increased IGFBP3 expression promotes PARPi resistance by enhancing DNA repair capacity. We verified increased levels of IGFBP3 RNA and protein in both OlapR models. We found that RNAi inhibition of IGFBP3 increases γH2AX and cleaved-PARP protein levels in the resistant models, which suggests accumulation of DNA double strand breaks leading to genomic instability and cell death. We discovered increased phosphorylation of EGFR and DNA-PKcs in the resistant cells. Furthermore, silencing/inhibiting IGFBP3 and EGFR reduces OlapR cell viability and resensitizes resistant cells to treatment. Our findings demonstrated that inhibiting IGFBP3 and EGFR aids in PARPi sensitivity in the resistant setting. Future work will utilize OlapR models to study how the IGFBP3/EGFR/DNA-PKcs protein complex promotes the development of resistance and serves as targets to improve PARPi therapeutics.

<<32>>   QUANTIFYING AND IDENTIFYING DNA ADDUCTS OF CARCINOGENS AND THERAPEUTICS

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The formation of covalently bound DNA adducts is considered both an initiator of mutation and carcinogenesis and a therapeutic approach to disrupt tumor cell replication with chemotherapy drugs such as the platins. DNA adduct formation is often a rare event, so sensitive analytical techniques are needed to detect and quantify adduct formation and evaluate adduct stability. Accelerator mass spectrometry (AMS) possesses the sensitivity to quantify adduct formation and persistence of environmentally relevant exposures to ubiquitous combustion products such as naphthalene and its metabolites. AMS has also been used to study whether a microdose of carboplatin can predict response to the full chemotherapy regimen. Using 14C-labeled substrates, adducts were quantified in whole DNA extracts of target tissues. The recent development at LLNL of a parallel accelerator and molecular mass spectrometry (PAMMS) system following a UPLC enables both AMS quantitation and molecular MS identification of parent compound and metabolite adducts on specific nucleotides from DNA digests. This work was performed in part at the National User Resource for Biological Accelerator Mass Spectrometry, which is operated at LLNL under the auspices of the U.S. Department of Energy under contract DE-AC52-07NA27344. Reviewed and released as LLNL-ABS-839629.

FRIDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>> METHODOLOGY MATTERS: A COMPARISON BETWEEN MAIL-IN SURVEYS AND COMMUNITY OUTREACH EFFORTS WHEN CAPTURING LATINO HEALTH RESPONSES IN AN NCI DESIGNATED CATCHMENT AREA

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Latinos are vastly affected by cancer and are unrepresented in research, clinical trials, and cancer efforts. To address this, catchment area population assessments (CAPA) are needed to understand their barriers and challenges. The UC Davis Comprehensive Cancer Center (UCDCCC) administered two similar CAPAs with different methodology. One used an address-based mailed questionnaire using probabilistic sampling (Westat) and the second used bilingual and bicultural research coordinators to engage community members through outreach and engagement efforts. A total of 361 participants is included in this study with 255 community-based and 106 mail-in surveys. Westat mail-in respondents are older ($p<0.0001$), more educated ($p=0.0403$), have higher income ($p<0.001$), and have more private insurance ($p=0.0002$). Those who are up to date with cervical and breast cancer screenings tend to have some form of health insurance, had a check-up within the year, were not told they have cancer, and investigated health information. Individuals are 50% less likely after one year ($p=0.1834$) and 73% less likely after two years ($p=0.0076$) to be up to date with cervical screening compared to those who had a check-up within the year. There is no association between cancer screening and survey type. We recommend a combination of both survey types in future data collection processes to allow for a richer dataset and larger sample size. Mail-in surveys help capture a "well-off" sample population. Community-based surveys allow for a higher response rate. This study serves as a basis for future intervention among targeted minority populations in our cancer center's catchment area.

<<2>> RACIAL/ETHNIC DISPARITIES IN RECEIPT OF GUIDELINE-CONGRUENT CARE AND SURVIVAL AMONG AYA PATIENTS WITH TESTICULAR GERM CELL TUMORS

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Background: Testicular germ cell tumors (TGCT) are the most common cancers in adolescent and young adult (AYA: 15-39 years) men in the U.S. and their incidence is increasing. Given the broad age range, AYAs are seen by both pediatric and adult practitioners and often do not receive uniform care. We described initial cancer care for AYAs with TGCTs, and factors associated with receipt of guideline-congruent care (GCC) and survival.

Methods: Using California Cancer Registry data, we identified AYAs diagnosed with a TGCT from 2004-2018 and defined GCC as surgery with or without chemotherapy and radiation depending on tumor histology and

stage. We used multivariable logistic regression and Cox proportional hazards models to measure factors associated with receipt of GCC and survival.

Results: Of the 11,335 patients with TGCTs, 46% were Hispanic, 45% were treated by urology/radiation oncology, 22% received all their care at a specialized cancer center (SCC), and 65% received GCC. Hispanic patients (vs. non-Hispanic (NH) White) and patients treated by hematology/oncology (vs. urology/radiation oncology) had decreased odds of receipt of GCC. Patients who received GCC and treatment from urology/radiation oncology (vs. hematology/oncology) experienced better survival. Patients who were older, of Hispanic and Black race/ethnicity (vs. NH White), with public insurance (vs. private), lived in low socioeconomic status neighborhoods, and received part/no treatment at a SCC (vs. all) had worse survival.

Conclusion: We found racial/ethnic disparities in the receipt of GCC and survival among AYAs with TGCTs. Future studies should investigate barriers to receiving GCC among different population subgroups.

<<3>>   REGULATION OF GENES LOCATED IN 6Q25 BY AN INDIGENOUS AMERICAN GENETIC VARIANT IN BREAST CANCER PATIENTS FROM PERU

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Breast cancer association studies identified a polymorphism in the 6q25 region, rs140068132A>G, that correlates with Indigenous American ancestry (IAA) and reduces the odds of developing breast cancer. The mechanisms by which this polymorphism confers a protective effect is unknown. We evaluated the association between rs140068132 and tumor gene expression in breast cancer patients with high IAA.

We exome-sequenced 242 breast tumors of patients from the PEGEN-BC study. Germline genotypes for rs140068132 were available (N=180 AA, 62 AG). Subtype was assigned by the pam50 method. Association between rs140068132 and gene expression in 6q25 was tested, adjusting by age at diagnosis and IAA.

Fifty-five tumors were classified as Luminal-A, 68 as Luminal-B, 63 as HER2-enriched and 56 as Basal-like. Among HER2-enriched tumors, rs140068132 was associated with ARMT1 (fold-change AA vs. AG (FC)=1.6, p=0.001), AKAP12 (FC=1.8, p=0.003), MTHFD1L (FC=0.72, p=0.003), CCDC170 (FC= 1.8,p=0.003), and RMND1 (FC=1.4,p=0.013). Among Luminal-B tumors, ARMT1 (FC=1.9,p=0.001), ESR1 (FC=1.4,p=0.04) and MTHFD1L (FC=0.8,p=0.02) were associated. Among Basal-like tumors, rs140068132 was associated with ESR1 (FC= 0.5, p=0.03). Analysis stratified by Luminal vs. non-Luminal tumors showed associations between genotype and ARMT1 (FC=1.7,p=0.001) and RMND1 (FC=1.4,p=0.03) among Luminals, while associations among non-Luminal tumors were identified for ARMT1 (FC=1.4,p=0.002), RMND1 (FC=1.3,p=0.01) and CCDC170 (FC=1.4,p=0.03).

The rs140068132-G variant regulates the expression of genes in the 6q25 region in a subtype-specific manner. One possible mechanism explaining its protective effect might be linked to the lower expression of MTHFD1L among G-allele carriers within HER2-positive subtypes. The expression of this gene is negatively associated with breast cancer survival.

<<4>> SURVIVAL AFTER CONTRALATERAL SECONDARY BREAST CANCER BY AGE GROUP IN CALIFORNIA

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Introduction: Secondary cancers account for 16% of new cancer diagnoses, with breast cancer (BC) most common and having poorer survival than primary BC (pBC). Additionally, BC survivors develop contralateral secondary BC (CSBC) at twice the rate as the general population. No studies to date have compared pBC survival to that of CSBC, which could influence counseling and treatment for patients with a history of prior BC.

Methods: Women (>15 years) diagnosed with pBC from 1991-2015 in the California Cancer Registry (n=377,176) were compared to those with CSBC (n=15,586) by age group (15-39, n=406; 40-64, n=6,814; >65, n=8,366). Multivariable logistic regression models assessed factors associated with CSBC. Multivariable Cox proportional hazards regression models assessed BC-specific survival, while accounting for the competing risk of death.

Results: Younger patients with CSBC more commonly underwent mastectomy (61%) and chemotherapy (54%) than middle-age (56%, 42%) and older women (46%, 16%). Across all ages, CSBC patients were less likely to have larger tumors (15-39, Odds Ratio (OR): 0.25, confidence interval (CI) 0.16-0.38; 40-64, OR 0.41, CI 0.37-0.45; >65, OR 0.46, CI 0.42-0.51) and lymph node positive disease (15-39, OR: 0.86, CI 0.69-1.08; 40-64, OR 0.88, CI 0.83-0.93; >65, OR 0.89, CI 0.84-0.94). For all ages, CSBC was associated with worse survival compared to pBC (15-39, Hazard Ratio (HR): 2.73, CI 2.30-3.25; 40-64, HR 2.13, CI 2.01-2.26; >65, HR 1.52, CI 1.43-1.61).

Conclusions: Worse survival after CSBC across all ages despite good prognostic factors suggests that CSBC may be biologically distinct and need treatment reconsideration.

<<5>> FORCE-INDUCED ACCUMULATION OF TENSIN AND LIM PROTEINS ALONG KERATIN FIBERS

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Mechanical force plays an important role in cell proliferation and differentiation. While the roles of the actin network in mechanotransduction have been well studied, the roles of the keratin network have not. Tensins are a family of proteins that have significant roles in cell focal adhesion, and possible roles in cancer metastasis. We found that cten, the fourth member of the tensin family, is responsive to externally applied forces and is recruited to keratin fibers upon cell stretch (Cheah et al., 2019). To further understand the role of the keratin network in mechanotransduction, we sought to identify other force-sensing proteins using live cell imaging and single-cell mechanical stretch assay. Tensin 3, a member of the tensin family, localized at focal adhesions and in the cytoplasm in the absence of force, but rapidly accumulated along keratin fibers in the presence of force. Force sensitive behavior was not observed in tensin 1 and 2, the other members in the tensin family. The sequence responsible for force-induced recruitment of tensin 3 (AA 595-1171) significantly differed from that of cten, suggesting a distinct molecular interface for each protein. Interestingly, other proteins such as LIMK1 (a

kinase and actin dynamics regulator) and LMO1 (a possible oncogene and transcription regulator) undergo a similar force-induced accumulation along the keratin fibers, rather than actin filaments. Since keratins are used as a diagnostic marker in cancer, the keratin network may be a critical force-sensing hub responsible for initiating a wide range of signaling cascades relevant to cancer.

<<6>> INVESTIGATING CORE BINDING FACTOR BETA'S ROLE IN PROTEIN TRANSLATION IN OSTEOSARCOMA

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Core binding factor beta (CBFβ) functions as a binding partner to the RUNX family of DNA binding transcription factors (RUNX1-3) and acts as an allosteric transcriptional co-activator. According to The Cancer Genome Atlas Program (TCGA) and Genotype-Tissue Expression (GTEx) datasets, high CBFβ expression is correlated with poor disease-free and overall survival across 17 cancer types, including sarcomas. Of particular interest to osteosarcoma research is CBFβ's interaction with RUNX2, the master regulator of bone growth and differentiation, and also dysregulated in aggressive OS. Previously, we generated a U2OS CBFβ_KO cell line, and in characterizing it we noticed a decrease in RUNX2 protein, but not mRNA, upon loss of CBFβ. A recent paper studying breast cancer cells, and these data generated in our lab in osteosarcoma cells, support CBFβ in having a novel role, as a regulator of protein translation. Proteasomal inhibition using MG132 was validated using Abnova Proteasome Activity Kit, and its influence on RUNX2 expression was assessed by western blotting (WB). U2OS wt and CBFβ_KO cells were transiently transfected with EGFP or CBFβ_FLAG in pcDNA3.1 using jetOPTIMUS followed by WB. Global protein translation was assessed by Thermo Fisher Click-iT OPP Alexa488 Kit, while RUNX2-specific translation was assessed using L-Azidohomoalanine labeling, immunoprecipitation of RUNX2, Click chemistry biotin conjugation and WB. Proteasome inhibition was successful with MG132, and did not recover low RUNX2 levels in CBFβ KO cells. Transfection of CBFβ_KO cells with CBFβ_FLAG recovered low RUNX2 protein expression. Loss of CBFβ decreases RUNX2-specific and global protein translation.

<<7>> MESENCHYMAL STEM/STROMAL CELL EFFECTS ON NEUROBLASTOMA CELLS GROWTH

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Purpose: Neuroblastoma is a pediatric cancer with survival of less than 50% for children with high-risk disease. Mesenchymal stem/stromal cells (MSCs) may represent a novel cellular delivery vehicle due to innate tumor homing. However, MSCs have demonstrated variable effects on tumor growth. We compared the effects of placental MSCs (PMSCs) and bone marrow-derived MSCs (BM-MSCs) on proliferation of neuroblastoma cells in culture.

Methods: Neuroblastoma cells were co-cultured with early-gestation PMSCs (n=9), term PMSCs (n=5) or BM-MSCs (n=4). Early-gestation PMSCs were grouped by neuroprotection effects as strong, intermediate, and weak (n=3 each). Neuroblastoma cell proliferation was assessed using an MTS assay and normalized to controls. A linear mixed effects model was used to assess the relationship between stem cell neuroprotection and neuroblastoma cell growth, as measured by fold change.

Results: Neuroblastoma cell proliferation varied between and within MSC groups (Figure). On average the term PMSC group had a 1.54 fold change in neuroblastoma cell proliferation, the highest amongst all groups and significantly higher growth effects than BM-MSCs (p=0.05). The lowest fold change was seen in the weak neuroprotective PMSC group with a 1.26 fold change, but this was not significantly lower when compared to BM-MSCs.

Conclusions: Effects of MSCs on neuroblastoma cell proliferation vary by group with term PMSCs demonstrating the highest proliferative effects and weak PMSCs promoting the least proliferation. Further ellucidation of the mechanism of MSC promotion of tumor cell proliferation may provide valuable insight into selection of cells best suited for drug delivery vehicles.

<<8>>   NATURAL COMPOUNDS URSOLIC ACID AND DIGOXIN EXHIBIT ANTI-CANCER EFFECTS THROUGH NUCLEAR RECEPTOR RORΓ-DEPENDENT AND -INDEPENDENT MECHANISMS

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Natural compounds such as ursolic acid (UA) and digoxin isolated from fruits and other plants display potent anti-cancer effects in preclinical studies. UA and digoxin have also been at several clinical trials for treatment of different cancers including prostate cancer, pancreatic cancer and breast cancer. However, they displayed limited benefit to patients. Currently, a poor understanding of their direct targets and mechanisms of action (MOA) in tumor cells severely hinders their further development. We previously identified nuclear receptor RORγ as a novel therapeutic target in castration-resistant prostate cancer (CRPC) and triple-negative breast cancer (TNBC). Previous studies implicated UA and digoxin as potential RORγ antagonists in modulating the functions of immune cells such as Th17 cells. Here we showed that UA displays a strong activity in inhibition of RORγ-dependent transactivation function, while digoxin exhibits no effect at clinically relevant concentrations. In prostate cancer cells, UA down-regulates RORγ-stimulated AR expression and AR signaling, whereas digoxin up-regulates AR signaling pathway. UA also showed potent anti-growth effects in AR-positive prostate cancer cells compared to AR-negative prostate cancer cells. In TNBC cells, UA but not digoxin alters RORγ-regulated cell proliferation and apoptosis gene programs. Together, our study shows for the first-time that UA, but not digoxin, acts as a natural antagonist of RORγ in prostate cancer and TNBC cells. Our finding that RORγ is a direct target of UA in specific type of cancer will help select patients with tumors that likely respond to UA treatment.

<<9>>   OLFACTOMEDIN-LIKE 3 PROMOTES MALIGNANT REATURES OF PATIENT-DERIVED GLIOBLASTOMA CELL LINES

Shafee Syed-Quadri, Dr. Ryan Toedebusch, and Dr. Christine Toedebusch

Human Glioblastoma (GBM) is an aggressive primary brain tumor with a 5-year survival rate of 5%. Resistance to surgical resection and radiation therapy requires exploration of novel and precise therapeutic targets to improve patient outcomes. Our laboratory has identified that olfactomedin-like 3 (OLFML3), a secreted glycoprotein, may be a promising target in GBM. OLFML3 has shown to promote angiogenesis and tumor cell malignancy in many non-CNS cancers. Importantly, we have demonstrated that OLFML3 promotes murine glioma cell proliferation, migration, and invasion. However, the effect of OLFML3 on human GBM cells is currently unknown. This study aims to test the hypothesis that OLFML3 increases the malignant features of human GBM cells. To test this hypothesis, we utilized two patient-derived GBM cell lines, as well as Immortalized U251 GBM cell lines. Cells were exposed to human recombinant OLFML3 (rhOLFML3; 1 & 10ng/mL, 48hrs.), followed by assessment of migration and invasion via transwell assay with or without Matrigel. Relative to vehicle-treated control cells, 10ng/mL rhOLFML3 patient-derived GBM cell migration ($p<0.001$) and invasion ($p<0.01$), as well as U251 cellular migration ($p<0.05$) were increased. These results suggest that OLFML3 may play a role in GBM tumorigenicity and warrants further study with additional cell lines. This study begins to characterize OLFML3's role in human glioblastoma cells, indicating its potential protumorigenic impact on tumor progression.

<<10>> PRE-CLINICAL EVALUATION AND FIRST-IN-DOG CLINICAL TRIALS OF INTRAVENOUS INFUSION OF PBMC-EXPANDED ADOPTIVE NK CELL THERAPY IN DOGS WITH CANCER

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Natural killer (NK) cells are cytotoxic immune cells capable of recognizing heterogeneous cancer targets without prior sensitization, making them promising prospects for use in cellular immunotherapy. Previously, CD5 depletion of peripheral blood mononuclear cells (PBMCs) has been used in dogs to isolate and expand a CD5dim-expressing NK subset prior to co-culture with an irradiated feeder line, but this can limit the yield of the final NK product. This study aimed to assess NK activation and preliminary clinical activity in first-in-dog clinical trials using unmanipulated PBMCs without CD5 depletion to generate our NK cell product. Median production of canonical NK cytokines, IFN-y and GM-CSF, at day 14 was over 5-fold greater in PBMC-expanded (IFN-y=316.7pg/mL, GM-CSF=267.0pg/mL) compared to CD5-depleted NK cells (IFN-y=59.6pg/mL, GM-CSF=48.7pg/mL) (P=NS). Sequencing data showed principal component sample variance based on time points and upregulation of NK pathways related to activation, crosstalk, and glycolytic function in both groups. PBMC-expanded NK cells for first-in-dog clinical trials showed sufficient expansion for multiple NK cell transfers at 7.5 x 106 cells/kg with no serious adverse events. We also observed preliminary data for efficacy, particularly in the allogeneic setting where peripheral blood gene expression significantly changed post-transfer and one dog survived 445 days post-treatment. Overall, the use of unmanipulated PBMCs appears safe and potentially effective for canine NK immunotherapy with equivalent or superior results to CD5 depletion in NK expansion, activation, and cytotoxicity. Our pre-clinical and clinical data support further evaluation of this technique as a novel platform for optimizing NK immunotherapy in dogs.

<<11>> LOW-DOSE SORAFENIB ENRICHES FOR CANCER STEM CELLS AND IS ASSOCIATED WITH ACCELERATED TUMOR PROGRESSION IN SOFT TISSUE SARCOMAS

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The cancer stem cell (CSC) hypothesis postulates that heterogeneous human cancers harbor a population of stem-like cells which are resistant to cytotoxic therapies, thus providing an important source of relapse following conventional therapies like chemotherapy and radiation (RT). CSC have been observed in multiple human cancers, and their presence has been correlated with worse clinical outcomes. Here, using multiple in vitro and in vivo models including primary sarcoma specimens at surgery, we observe that sarcoma CSCs appear to paradoxically respond to the tyrosine kinase inhibitor sorafenib at low doses with increased proliferation and stem-like function whereas anti-viability effects dominated at higher doses. Importantly, sarcoma patients receiving neoadjuvant sorafenib plus RT on a clinical trial showed increased CSCs post-therapy, and higher ALDH score post therapy was associated with worse metastasis-free survival. Taken together, these data suggest that low dose sorafenib may promote the CSC phenotype in sarcomas with clinically significant effects.

<<12>> ROLE OF BHLHE40 IN THERAPY-RESISTANT PROSTATE CANCER

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Background: The basic helix-loop-helix factor BHLHE40 is a transcriptional repressor whose subcellular localization regulates tumor suppressive vs oncogenic properties. Its role in prostate cancer (PCa), outside of PC-3 cells, has not been reported.

Methods: Formalin fixed paraffin embedded (FFPE) primary prostate tumor and surrounding non-tumor tissues of 78 patients who underwent radical retropubic prostatectomy at VA Northern California Health Care System were used; 51 metastatic lesions from patients who were diagnosed with metastatic PCa (mPCa) between 1995 and 2013 were obtained from the archives of Mayo Clinic. LNCaP and C4-2 cells were used for in vitro experiments including immunofluorescence and chromatin immunoprecipitation.

Results: BHLHE40 was nuclear in non-malignant areas vs. cytoplasmic in malignant areas; cytoplasmic BHLHE40, nuclear AR, Ki67 were highly correlated in tumors. Nuclear BHLHE40 increased in mPCa compared to localized tissue and correlated with survival.

LNCaP and C4-2 cells mostly expressed high levels of cytoplasmic BHLHE40, which localized in the nucleus in response to androgen deprivation. Overexpressing BHLHE40 reduced C4-2 proliferation, with only a modest effect in LNCaP cells; conversely, BHLHE40 knock-down increased proliferation. Chromatin-immunoprecipitation (ChIP) indicated that AR binds to an androgen-responsive element in LNCaP cells but binding is lost in C4-2 cells. Anti-androgens bicalutamide (BIC) and enzalutamide (ENZA) inhibited BHLHE40 expression in LNCaP cells but not in C4-2.

Conclusions: Together, these results indicate that AR activity regulates BHLHE40 localization. BHLHE40 regulated cell cycle progression in CRPC cells where it is cytoplasm localized, but not in hormone sensitive PCa where it is localized in the nucleus.

<<13>> THE C-TYPE LECTIN DOMAIN OF CD62P (P-SELECTIN) INTERACTS WITH INTEGRINS AND POTENTIALLY MEDIATES CANCER CELL-ENDOTHELIUM INTERACTION, AN INITIAL STEP IN CANCER METASTASIS.

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CD62P (P-selectin) is confined to the inside of platelets and endothelial cells, and is translocated to the surface upon activation of platelets or endothelial cells. In current models, CD62P recognizes sialyl-Lewis X on PSGL-1 and mediates rapid rolling of leukocyte over vascular surfaces during the initial steps in inflammation and cancer metastasis. Docking simulation using integrin αvβ3 as a target predicted that the C-type lectin domain of CD62P is a potential integrin ligand. It has not been tested if CD62P binds to integrins. Here we describe that the lectin domain of CD62P specifically bound to soluble integrins αvβ3, αIIbβ3, α4β1 and α5β1. Known inhibitors of CD62P-PSGL-1 interaction did not suppress the binding of the lectin domain to integrins. We

found that the R16E/K17E mutation in the predicted integrin-binding interface of the lectin domain strongly inhibited CD62P binding to αIIbβ3 and αvβ3 in 1 mM Mn2+. R16E/K17E is outside of the glycan binding site. Mutating Glu-88 to Asp (the E88D mutation) in the lectin domain, which is known to strongly disrupt glycan binding, only slightly affected integrin binding, indicating that glycan binding and integrin binding sites are distinct. Also, the lectin domain of CD62P supported cell adhesion in a cation-dependent manner. CD62P-integrin interaction is potentially important since integrins are widely expressed compared to PSGL-1, which is limited to leukocytes. These findings indicate that CD62P-integrin interaction plays potentially important role in a wide variety of cell-cell interaction (including cancer cell-endothelial cell interaction) in addition to CD62P-glycan interaction.

<<14>>   THE IMPACT OF METALS ON THE STRUCTURE AND DYNAMICS OF THE TAIL DOMAIN OF VIMENTIN

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Vimentin intermediate filaments (IFs) are an integral component of the cell cytoskeleton and play key roles in cell architecture and migration. The overexpression of vimentin has been observed in various epithelial cancers and the reorganization of its filaments have been linked to increased cellular migration and invasion. As a result, there is growing interest in investigating the potential of vimentin as a target for cancer therapy. However, the exact mechanisms that drive filament reorganization remain poorly understood. The binding of metal ions to the tail domain of vimentin has shown to influence filament structure and organization, but atomic-level characterization of the structure and protein-metal interactions of intact vimentin IFs is lacking. To determine the metal binding mechanism of the tail domain and the effects on structure and dynamics of vimentin IFs, a 'divide and conquer' approach involving parallel investigations of tail domain peptide and protein fragments is employed. For the first time, the expression and synthesis of the vimentin tail domain protein and the c-terminal 11-mer peptide are reported. Preliminary results from mass spectrometry and UV-Visible absorption spectroscopy suggest the binding of Cu(II) to the 11-mer peptide. Future studies include determination of amino-acid specific interactions and the structural changes upon metal binding using point-mutation studies, nuclear magnetic resonance, and circular dichroism spectroscopy. The outcomes of this work will serve as an experimental framework for characterizing the structure and protein-metal interactions of other IFs, and aid in the development of IF-based therapeutic agents and cancer treatments.

<<15>>   INTRAOPERATIVE DETECTION OF IDH-MUTANT GLIOMA SUBTYPE USING FLUORESCENCE LIFETIME IMAGING

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In-situ identification of IDH-mutant glioma subtype can enable modifications of clinical and surgical strategies. IDH-mutant astrocytoma benefit from more aggressive resection than grade-matched oligodendroglioma, which have a more favorable response to post-surgical chemotherapy. Preoperative MRI and intraoperative histology cannot precisely determine glioma subtype. There is a need for real-time identification of adult-type diffuse IDH-mutant glioma subtypes to aid the neurosurgeon's decision-making during resection surgery. Fluorescence lifetime imaging (FLIm), where tissue autofluorescence can be used as an indicator to distinguish among brain tumor tissue types intraoperatively, could aid this process. Here, we report the use of label-free FLIm in distinguishing IDH-mutant glioma subtypes. The FLIm system (excitation: 355 nm; emission

bands: 390/40 nm, 470/28 nm, 540/50 nm) was used to scan brain tissue from the resection margins of glioma patients undergoing tumor resection. Fluorescence lifetimes were extracted and analyzed by constrained least-squares deconvolution with Laguerre expansion method. FLIm data was validated with histopathology of collected biopsies. Current results show that FLIm provides optical contrast between tumor and normal white matter, and between IDH-mutant astrocytoma (N=5 patients) and oligodendroglioma (N=5 patients). Tumors showed shorter lifetime values in the 470-nm (3.7 ± 0.6ns) and 540-nm (3.3 ± 0.7ns) channels, which are associated with NAD(P)H and FAD fluorescence, respectively, than healthy white matter (470-nm: 4.7 ± 0.3ns; 540-nm: 4.3 ± 0.4ns, $p<0.01$). Oligodendroglioma had significantly shorter lifetimes in the metabolic channels (470-nm: 3.4 ± 0.1ns; 540-nm: 2.9 ± 0.3ns) than astrocytoma (470-nm: 4.3 ± 0.2ns; 540-nm: 4.0 ± 0.3ns, $p<0.01$). Together, these results demonstrate the potential of FLIm as an intraoperative tool in IDH-mutant glioma diagnosis.

<<16>> THE ROLE OF INTERVENTIONAL MRI FOR SELECTIVE DRUG DELIVERY IN BRAIN CANCER

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Glioblastoma multiforme (GBM) cancer remains amongst the uncurable malignancies in the brain with a very poor prognosis. Current treatments include tumor resection followed by simultaneous radiotherapy and chemotherapy. However, the blood brain barrier (BBB) hinders the delivery of anticancer agents. To meet this need, novel therapies are being developed that can cross the BBB, however their delivery is attenuated at the tumor site because of non-specific uptake throughout the body when infused systemically. A proposed solution is to use endovascular selective intra-arterial infusion (ESIAI), an approach that leverages image guided catheters to deliver the anti-tumor drug directly via the tumors main supply vessel. Although magnetic resonance imaging (MRI) is the modality of choice for this task, it remains unused because of safety and visualization concerns of metallic endovascular devices within the MRI. The alternative is x-ray fluoroscopy, but it requires the time-consuming task of transferring patients between scanners, which also necessitates more space to house both modalities, making it impractical and expensive. The challenge is to safely visualize the endovascular devices in MRI. In this proposed work I plan to implement a method for safe imaging of endovascular devices in the human brain to make ESIAI a practical cancer therapy. The aims of the proposed work are to demonstrate the device visualization in phantoms, to demonstrate the effectiveness of selective drug delivery in vivo in a rat model of GBM, and to develop imaging protocols to accurately identify the tumor location and extent of infiltration.

<<17>> A PILOT STUDY ON RETINAL FEATURES AND COGNITIVE FUNCTION IN PATIENTS WITH LOW GRADE GLIOMAS

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Background: Retinal structure and vascular changes are used as biomarkers for preclinical Alzheimer disease. We conducted a cohort study to evaluate the feasibility of obtaining these data in patients with low-grade gliomas (LGGs) who completed chemoradiation therapy with and without self or family reported cognitive concerns.

Methods: Optical coherence tomography (OCT) and angiography (OCTA, OptoVue, Inc.) images were obtained from 6 LGG patients and 2 healthy controls using 4.5 x 4.5 mm peripapillary and 6x6 mm macular scan patterns. We measured OCTA parameters including radial peripapillary capillary density for the peri-optic disc region, whole macular density, and foveal avascular zone (FAZ).

Results: We analyzed two eyes of two control subjects, an LGG patient with normal cognition, and 5 LGG patients with cognitive impairment (mean age 45 years, range of 3 months to 10 years after chemoradiation). Both controls had normal eye exams. Average retinal nerve fiber layer thickness was thinner in patients with and without cognitive dysfunction (104 um and 106 um, respectively) than controls (123 um). A similar pattern was seen in macula thickness (283 um and 290 um vs. 325 um). The average peripapillary vessel densities were lower in patients with and without cognitive dysfunction (47.7% and 48.3%, respectively) than controls (51.9%). The whole macular vessel densities were similar in three groups (46.7 %, 48.0%, and 48.0 %). Average FAZs were larger in patients with cognitive dysfunction (0.254 mm2) than the patient with normal cognition (0.204 mm2) and controls (0.226 mm2).

Conclusions: Retinal architecture and microvascular changes measured by OCT/OCTA is feasible in LGG patients after chemoradiation. A larger prospective study is needed to investigate the role of OCT/OCTA in detecting peripapillary and perifoveal changes in brain tumor patients with treatment-associated cognitive dysfunction.

<<18>> A WESTERN-STYLE MIMICKING HIGH-FAT DIET INCREASES EARLY STAGE PANCREATIC CARCINOGENESIS IN A KC MURINE MODEL

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Pancreatic cancer is the 3rd leading cause of cancer-related deaths in the USA. Previous studies have indicated that high-fat diets, but also high sugar diets, accelerate pancreatic carcinogenesis. Although the link between increased body fatness and pancreatic cancer risk is apparent, the impact of diets resembling a Western-style diet with a high omega-6 to omega-3 fatty acid (FA) ratio, remains unclear. The objective was to determine the impact of a high-fat diet, that mimics the Western-style diet with a ratio of 10 parts omega-6 FA to each omega-3 FA, on early stages of pancreatic carcinogenesis in a clinically relevant, genetically engineered LSL- KrasLSL-G12D; Ptf1aCre/+ (KC) model of pancreatic cancer. Cohorts of male and female KC mice were weaned and at five weeks of age, the mice were randomly assigned to either a control diet (CD) group or a diet induced obesity (DIO) group and fed their diets until three months of age. After 8 weeks on their diets, DIO-fed mice had significantly higher body weight and fat mass, and significantly lower lean, compared to CD-fed mice. Additionally, male, but not female, DIO-fed mice had a significantly larger pancreas weight. Upon histological analysis, DIO-fed mice had a significantly increased rate of acinar-to-ductal metaplasia (ADM). In addition, there were high serum concentrations of leptin, insulin, the pro-inflammatory cytokines IL-6, IL-10 and TNF-α in DIO fed mice. Our results indicate that feeding a high-fat diet for 8 weeks may promote pancreatic carcinogenesis by increasing body fatness, ADM, and levels of chemical mediators.

<<19>> BIOENGINEERING MICRORNAS TO MODULATE SOLUTE CARRIER TRANSPORTERS

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MicroRNA (miRNA) are genome-derived noncoding RNAs (ncRNAs) with crucial roles in the control of posttranscriptional gene regulation, including many cancer-related genes. Solute carrier (SLC) transporters are a diverse family of facilitative or secondary active transporters responsible for the influx and efflux of a wide array of substrates, including essential nutrients and medications. Some miRNAs have been shown to directly regulate specific SLCs. Additionally, there is rising interest in developing ncRNA therapeutics, which has been substantiated by the US Food and Drug Administration approval of five siRNA medications. However, RNA research and drug development commonly uses chemically synthesized RNA mimics with extensive modifications that are not present in natural RNAs. The Yu laboratory has established a novel method to produce bioengineered RNA agents (BioRNAs) in Escherichia coli. In this study, we aimed to compare the efficacy of htRNAGly/hsa-pre-miR-34a and htRNALeu/hsa-pre-miR-34a carriers to produce BioRNAs and utilize novel BioRNAs to explore miRNA-controlled regulation of SLCs. A set of 20 BioRNA/miRNAs were

designed and overexpressed in E. coli, among them 10 were based on the htRNAGly/hsa-pre-miR-34a carrier and 10 paired miRNAs on the htRNALeu/hsa-pre-miR-34a carrier. Fast Protein Liquid Chromatography was then used to purify individual recombinant miRNAs. High Performance Liquid Chromatography and Endotoxin Assay Kit were used to determine purity and endotoxin level of each BioRNA, respectively. Our data demonstrate the robustness of tRNA/pre-miRNA-based recombinant miRNA platform technology and applications of bioengineered RNAs to general biomedical research.

<<20>> DEVELOPMENT OF A SIMPLE AND REPRODUCIBLE CELL-DERIVED ORTHOTOPIC XENOGRAFT MURINE MODEL FOR NEUROBLASTOMA

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Background: Neuroblastoma is a rare childhood cancer with remarkable heterogeneity and a tendency to undergo cellular and genomic mutations. Development of targeted therapies is essential for improved treatment. Patient-derived xenografts (PDX) and genetically-engineered mouse models (GEMM) are reliable murine models for oncologic research; however, these models are resource -intensive, expensive, and require significant experience to develop and maintain. We developed an orthotopic xenograft murine model of neuroblastoma that utilizes immortalized human cells, requires minimal equipment, and is easily reproducible.

Methods: NOD scid gamma mice underwent orthotopic injection of two million human neuroblastoma cells from the Children's Oncology Group Childhood Cancer Repository (cell line NB1643) directly into the adrenal gland via an open retroperitoneal surgical approach. Mice were monitored by ultrasound for tumor growth until the tumor volume reached the volume of the ipsilateral kidney. Tumor presence was confirmed by necropsy and histologic analysis.

Results: Ten mice underwent surgery. Two died due to anesthetic or surgical complications. Average anesthesia time was thirty minutes. Ultrasound successfully characterized tumor growth in all mice. Average time to target tumor size was five weeks. Gross pathologic and histologic analysis confirmed neuroblastoma in all mice.

Conclusion: A cell-derived orthotopic xenograft murine model can be successfully used to create an in vivo model of neuroblastoma. This model can be utilized in environments where PDX or GEMM models are not feasible or for initial pilot studies. Further directions include expansion and optimization of the current model, as well as exploration of percutaneous orthotopic tumor cell injections.

<<21>> FUNCTIONAL GENETICS OF APR-246 RESCUABLE TP53 MUTANTS

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TP53, often referred to as the guardian of the genome, encodes for the p53 tumor suppressor protein, and it is one of the most frequently mutated genes in human cancers. Two cancer types with the highest prevalence of TP53 mutations are high-grade serous carcinoma (96%) and lung squamous cell carcinoma (80%). About 90% of TP53 mutations reside in the DNA binding domain and consist of single-base substitutions, with a majority resulting in missense mutants.

APR-246 is an investigational drug, currently in clinical trials for the rescue of p53 mutants in hematologic cancers and solid tumors. This small molecule drug is proposed to bind mutant p53 to promote

thermodynamic stabilization of the protein. This allows the mutant p53 to regain functional confirmation and consequentially regain wild type p53 functionality. There has yet to be a systematic functional genomic screening of APR-246 rescuable p53 mutants.

Our research goal is to address this critical gap in actionable clinical knowledge using a TP53 mutagenesis library. This pooled lentiviral library contains 24,823 codon variants, consisting of missense and nonsense variants along the entire TP53 gene. After stably transducing this library into p53-null cancer cell lines, we will perform a functional screening against APR-246. Following the treatment with a sublethal dose of APR-246, we will use Illumina sequencing to compare the variant representation in treated versus untreated control samples. Identifying which p53 mutants are able to be rescued by APR-246, allows us to gain actionable clinical insight as to which patients may benefit from the drug.

<<22>> FUNCTIONAL OUTCOMES OF LIP-SPLIT MANDIBULOTOMY FOR ACCESS OF ORAL AND OROPHARYNGEAL TUMORS

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Introduction: Lip-split mandibulotomy is the treatment of oropharyngeal tumors that cannot be fully resected using less invasive approaches. This study assessed postoperative morbidity through swallowing outcomes, such as gastrostomy tube (GT) dependence and objective swallowing measures, as well as cancer-related outcomes.

Methods: A retrospective review was conducted on patients who underwent lip-split mandibulotomy for an oropharyngeal malignancy between 2015 and 2022. Demographics, tumor characteristics, comorbidities, and treatment outcomes were collected.

Results: 18 patients (11 men and 7 women, mean age 63.7 years) were identified. Duration (in days) of gastrostomy tube dependence was longer in patients with a BMI under 25 vs over 25 (530.22 vs 161.67, p=0.09). Longer GT placement was required for those with oral cavity tumors as compared to oropharyngeal tumors (527.83 vs 286.11, p=0.29) and those with stages T3 or higher as compared to T2 or lower (520.22 vs 176.67, p=0.12). The average Eating Assessment Tool-10 score 1-month after surgery was indicative of dysphagia at 21.1 points. Common complications were hematomas (16.67%) and surgical dehiscence (11.11%), although 66.67% of patients did not have any complications within 30 days of surgery. At the latest follow-up, 66.67% of patients were disease-free and 72.22% of patients remained alive.

Conclusions: Patients should be advised regarding post-treatment dysphagia, although this varies based on factors such as malnourishment (BMI <25) and staging. Aside from swallowing impairment, lip-split mandibulotomy demonstrated an excellent perioperative survival rate and a low rate of serious complications. This study suggests it remains an appropriate option for advanced tumors.

<<23>> IMMUNE MODELING OF COLORECTAL LIVER METASTASES (CRLM) USING AN EX-VIVO 3D TUMOR-ON-A-CHIP MODEL

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Background: Colorectal cancer (CRC) mortality is mainly due to metastases. Most CRLM patients have microsatellite stable (MSS) tumors and do not respond to immunotherapy. We aimed to create a vascularized "tumor-on-a-chip" platform of patient-derived organoids (PDO) from CRLM as a pre-clinical model for investigating the tumor microenvironment and response to immunotherapies.

Methods: CRLM specimens with patient-matched human peripheral blood mononuclear cells (PBMCs) were collected. Tumor samples were dissociated by mechanical and enzymatic digestion and cultured in growth media for 6-8 weeks to generate PDOs. IHC was performed of matched tumors and PDOs to determine epithelial cells (CK18), fibroblasts (vimentin), immune cells (CD45), and endothelial cells (CD31). To test the feasibility of the 3D-chip for tumor growth, PDOs were cultured and introduced into a microfluidic device. Labelled PBMC were perfused into the device to evaluate extravasation using confocal microscopy.

Results: Eight tumor samples were collected to create PDOs with an 80% success rate (20%: slow growth/non-viable associated with prior chemotherapy). PDOs were successfully recycled through a freeze/thaw cycle for future use, a critical step for reproducibility. IHC showed the cell composition in the PDO was predominantly epithelial tumor cells with sparse stromal and immune cells. A time lapse video over 2 hours demonstrates PBMC extravasation/migration into the PDOs, demonstrating feasibility of populating PDOs with patient-matched leukocytes.

Conclusion: We demonstrate a proof-of-concept tumor-on-a-chip platform with patient matched immune cells. This system provides a platform for pre-clinical modeling of the tumor microenvironment, including the immune cell component, to further explore novel immunotherapeutic strategies.

<<24>> INCIDENCE OF INTRACRANIAL HEMORRHAGE IN GLIOMA PATIENTS WITH VENOUS THROMBOEMBOLISM CONVERTED FROM LMWH TO APIXABAN

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Venous Thromboembolism (VTE) occurs in approximately 15-30% of patients with glioma who are treated with therapeutic anticoagulants. Anticoagulation treatment increases the incidence of intracranial hemorrhage (ICH) with variable incidence between studies 1.9% to 20s%. The "common practice" treatment for VTE in glioma patients includes subcutaneous administration of low molecular weight heparin (LMWH, enoxaparin) injection, which requires daily self-injection.

The goal of this project is to evaluate the incidence of intracranial hemorrhage in glioma patients with VTE converted from LMWH to Apixaban. We hypothesize that patients with brain tumors and Venous Thromboembolism can be converted safely from LMWH to Apixaban. To examine this hypothesis, we will enroll adult patients with pathologically confirmed supra-tentorial glioma and VTE, patient must have been treated with LMWH for ≥ 5 days. We will exclude patients with bleeding diathesis, severe hypersensitivity to Apixaban or pregnant or unable to provide informed consent:

Primary Objective: To estimate the incidence of ICH in glioma patients with history of VTE after the conversion from LMWH to oral Apixaban

Secondary Objective: To estimate the incidence of recurrent VTE in glioma patients with history of VTE after the conversion from LMWH to oral Apixaban

To our knowledge, this is the first of its kind study to estimate the risk of ICH in glioma patients with VTE treated with oral anti-coagulation. Successful completion of our trial will provide answers to an important clinical question that could allow our patients using more convenient yet effective treatment by establishing and implementation of best practices.

<<25>> NOVEL BIOENGINEERED MIR-1291 MODULATES THE EXPRESSION OF XENOBIOTIC NUTRIENT TRANSPORTERS AND METABOLIC ENZYMES TO CONTROL CANCER CELL METABOLISM

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Carcinoma cells are metabolically reprogrammed to access excessive nutrients under the tumor microenvironment towards disease progression. Therefore, controlling nutrient transport and metabolism in cancer cells is a promising therapeutic strategy. Our previous studies have revealed that microRNA-1291-5p (miR-1291) acts as a tumor suppressor whereas downregulated in pancreatic cancer (PC) cells. The current study is to delineate the role of miR-1291 in PC cell metabolism and develop miR-1291-based therapy. We first employed our unique RNA bioengineering technology to achieve high-yield production of a fully humanized biologic miR-1291 (BioRNA/miR-1291) molecule. RNA sequencing and proteomics studies revealed that BioRNA/miR-1291 was selectively processed to miR-1291 to modulate the transcriptome and proteome of PC cells. PNPO, a rate-limiting enzyme for the synthesis of vitamin B6 (VB6), was validated as a direct target of miR-1291. Furthermore, miR-1291 was showed to target the amino acid transporter SLC7A5/LAT1 and control its expression. Downregulation of PNPO, LAT1, GLUT1 protein expression by recombinant miR-1291 led to sharp alteration of homeostasis of glucose, amino acids, and VB6 in human PC cells and subsequently, suppression of glycolysis capacity and mitochondrial function as well as increase of oxidative stress. Combination treatment with BioRNA/miR-1291 and 5-FU exerted strong synergism in the inhibition of PC cell and organoid proliferation in vitro. In addition, miR-1291 mono- and combination therapy were effective to control tumor growth in PC patient-derived xenograft (PDX) mouse models. These results demonstrate a critical role for miR-1291 in the regulation of PC cell metabolism which provide insight in developing new therapeutic strategies for PC.

<<26>> NOVEL HSP70 INHIBITORS IMPROVE ENZALUTAMIDE TREATMENT IN PROSTATE CANCER

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Ubiquitin proteasome system is suppressed in enzalutamide resistant prostate cancer cells and that the HSP70/STUB1 machinery is involved in AR and AR variant protein stabilization. Targeting HSP70 could be a valuable strategy to overcome the resistance of androgen receptor signaling inhibitors (ARSI) in advanced prostate cancer. A novel HSP70 inhibitor JG98 significantly suppressed drug resistant C4-2B MDVR and CWR22Rv1 cell growth and enhanced enzalutamide treatment. JG98 also suppressed the PDX derived organoid growth and induced organoid death in a dose dependent manner. Mechanistically, JG98 suppressed AR/AR-V7 expression in resistant cells and promoted STUB1 entering into the nucleus and bound to AR-V7. Knockdown of STUB1 significantly diminished JG98 anti-cancer effect. A more potent HSP70 inhibitor JG231 was developed from JG98. JG231 significantly improved the drug solubility and showed better pharmacokinetic characteristics than JG98. Moreover, JG231 effectively suppressed the cell growth and enhanced enzalutamide treatment in resistant cells and PDX derived prostate cancer cells. The HSP70/STUB1 machinery involved in AR/AR-V7 regulation and enzalutamide resistance. Targeting HSP70 by novel HSP70 inhibitors overcome the ARSI resistance and improve their therapy.

<<27>>   OSTEOTROPIC REGULATION OF BHLHE40 IN BONE

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Background: BHLHE40 is a transcriptional repressor that is dysregulated in breast and hepatocellular carcinomas. Despite broad expression, its function and regulation in skeletal cells is limited. Bhlhe40 increases under chondrogenic or osteogenic differentiation of mesenchymal stem cells and adenoviral-mediated Bhlhe40 induces chondrogenic and enhances osteogenic differentiation. Within, we sought the impact of osteoregulatory agents on Bhlhe40 expression and transcriptional activity.

Methods: Pre-osteoblastic murine MC3T3-E1 cells or the rat osteosarcoma UMR106.1 cells were cultured under standard conditions and trypsinized regularly. MC3T3-E1 cells were treated with 100nM hPTH(1-34) or 100ng/mL BMP-2; total RNA was collected 3, 6, or 24h later for qPCR analysis. BHLHE40 transcriptional activity was monitored using luciferase reporter plasmids transiently transfected into UMR106.1 cells.

Results: In MC3T3-E1 pre-osteoblasts, 100nM hPTH(1-34) increased Bhlhe40 expression after 3, 6, or 24h; in contrast, BMP-2 failed to elicit a consistent impact. To elaborate transcriptional impact of Bhlhe40 on gene expression, UMR106.1 cells were transiently transfected a plasmid containing four BHLHE40 consensus binding sites cloned upstream of luciferase reporter gene; subsequently, transfected cells were treated with PTH, TGF-□1, BMP-2, or the hypoxia mimetic desferoxamine. Transcriptional activity increased in response to PTH and hypoxia mimetic, whereas neither BMP-2 not TGF-□1 reproducibly impacted luciferase levels.

Conclusions: Bhlhe40 appears to be reciprocally regulated in skeletal cells, wherein PTH and the hypoxia mimetic DFO increase Bhlhe40 expression and transcriptional activity in osteogenic cells. Given its emerging role in cancer progression and frequent metastasis to bone, understanding Bhlhe40 expression and function in bone may suggest novel metastatic mechanisms.

<<28>>   RECEPTOR TYROSINE KINASE (RTK)/ALK INHIBITOR ALECTINIB BLOCKS NEUROENDOCRINE PROSTATE CANCER CELL GROWTH

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Neuroendocrine prostate cancer(NEPC) is an aggressive subtype of prostate cancer that can occur de-novo or arise through anti-androgen receptor (AR) drug treatment.Currently there is no effective treatment for NEPC. Alectinib is a receptor tyrosine kinase inhibitor that targets the anaplastic lymphoma kinase receptor(ALK) and is an FDA-approved drug. Alectinib has been used to treat non-small cell lung cancer (NSCLC) in patients who developed resistance to RTK inhibitor Crizotinib. Here we evaluate whether alectinib could work as a therapeutic drug to treat NEPC using de-novo and induced NEPC prostate cancer cell lines((42D, NCI-H660, C42B-enzr, and C42B).Treating these cells with alectinib we observed that alectinib effectively inhibited cell growth in all four cell lines. Our further analysis revealed that alectinib affected ALK signaling. Downstream targets of ALK signaling STAT3 and AKT phosphorylation decreased in cells treated with alectinib. Moreover, NEPC cellular marker expression such as enolase2, BRN2, and ASCL1 decreased with alectinib treatment. Lastly, we evaluated a panel of therapeutic compounds that could work in conjunction with alectinib and we found that CMC272, an inhibitor of epigenetic regulator G9a/DMNT, had a synergistic effect with Alectinib in 42D cells but not in NCI-H660 cells. Our current results demonstrate that alectinib can be effective in inhibition

of NEPC cell growth and suggest that alectinib can potentially be a therapeutic treatment for patients with NEPC.

<<29>>   ROLE OF MIR-7-5P IN MITOCHONDRIAL FUNCTION

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Non-Small Cell Lung Cancer (NSCLC) makes up 84% of all lung cancer cases and lack of effective treatment options contribute to low survival rates. RNA interfering (RNAi) microRNA (miRNA) provide researchers with a versatile alternative to modulate target gene expression and manipulate miRNA profiles to combat disease. Of these, tumor suppressive miR-7-5p (miR-7) is reduced in NSCLC. Notably, miR-7 downregulates genes important in metabolism and mitochondrial function including EGFR and VDAC1, and it is a putative regulator of mitochondrial genes AGK, PPIF, and DTYMK. Most available miRNA mimics on the market are chemically synthesized in vitro and contain extensive modifications. By contrast, our laboratory has developed a novel technology to bioengineer RNAi agents (BioRNA) in vivo utilizing specific tRNA/pre-miRNA carriers. Using this technology, we aim to develop BioRNA/miR-7 as a novel, bio-synthesized anticancer agent that functions through endogenous RNAi mechanisms to regulate mitochondrial metabolism. Thus far, we have successfully produced BioRNA/miR-7 in vivo and attained a purity of 98.7% and endotoxin level of 0.68 (EU/µg). Additionally, we validated the processing of BioRNA/miR-7 to mature miR-7-5p in human NSCLC cells and assessed its capability to regulate known target gene expression in comparison to a commercial mimic. Furthermore, we established the effect of BioRNA/miR-7 on reducing cell viability and altering mitochondrial localization and morphology. The success of the BioRNA technology together with previous preliminary data on miR-7 suggests that miR-7 plays an important role in mitochondrial functions, and BioRNA/miR-7 may be developed as a new therapeutic RNA for the treatment of NSCLC.

<<30>>   SALMETEROL XINAFOATE PREFERENTIALLY ERADICATES GLIOMA CELLS, IN VITRO

Orli Algranatti, James Angelastro, Ji Yae Lee

Epinephrine and norepinephrine stress hormones promote cancer progression by activating the α and β-adrenergic receptors. As supported by epidemiological studies, blockage of these receptors, primarily β-adrenergic receptors, inhibits the growth of several cancer types. Glioblastoma (GBM) expresses β-adrenergic receptors (significantly β-2-adrenergic receptors), and GBM accounts for 50% of central nervous system cancers, with a survival time of 15 months after Standard of Care therapeutic intervention, which is surgical resection, radiation, chemotherapy, or all three. Our hypothesis is based on the interference with the β-2-adrenergic receptor's function, which will destroy GBM cells.

Our highest potency drug, salmeterol xinafoate, is the β-2-adrenergic receptor biased agonist that activates the G-protein pathway rather than the β-arrestin pathway. Biased agonists activate signaling through the G-protein or the β-arrestin pathway of G-Protein Coupled receptors (i.e., β-adrenergic receptor). Our findings show that salmeterol xinafoate leads to cell death of glioma cells but spares healthy neurons at similar drug doses. The siRNA knockdown of the β2-adrenergic receptor corroborates our results of a loss of survival in LN229 and GBM5 glioma cells. In glioma cell lines [LN229, GBM5, and GBM12], the mechanism of action appears to be through the downregulation of survivin. In the LN229 cell line, salmeterol xinafoate was shown to trigger the activation of cleaved caspase-3. Chronic Obstructive Pulmonary Disease is the current use of this drug. Repurposing this FDA-approved drug for GBM could be fast-forwarded into clinical trials because drug safety has previously been determined.

<<31>>   EVALUATION OF CYTOTOXICITY, SAFETY AND MAMMARY TISSUE RETENTION OF THERMOSENSITIVE SYSTEMS CONTAINING NANOSTRUCTURED LIPID CARRIERS FOR CO-ADMINISTRATION OF PACLITAXEL AND TRIBUTYRIN AS A NEW STRATEGY FOR THE LOCALIZED TREATMENT OF BREAST CANCER

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Nanostructured lipid carriers (NLC) co-encapsulating paclitaxel and tributyrin (for cytotoxicity potentiation) developed for intraductal delivery were evaluated for cytotoxic effects in vitro and for mammary tissue retention after administration in rats. The nanoencapsulation influence on drug cytotoxicity was evaluated through MTT assay. Formulation toxicity was assessed on Galleria mellonella larvae prior to its administration in rats. Rhodamine B-loaded nanoparticles (0.5%, w/w) were obtained to evaluate nanoencapsulation influence on mammary tissue retention using an in vivo imaging system (IVIS Spectrum, Waltham, MA); NLC was incorporated into a thermosensitive poloxamer 407 gel (11%, w/w) to further improve retention. Local irritation was assessed by histological examination of the mammary tissue surrounding the administration site. Tributyrin reduced formulation IC50 value by 3-fold, compared to a control carrier containing tricaprylin (liquid lipid); paclitaxel addition further reduced IC50 values up to 8 and 2.9-fold in MCF7 and T47D cell lines. NLC didn't increase drug cytotoxicity (IC50 27–30 mM) compared to drug solution (IC50 28–33 mM), which was attributed to slower drug release from the lipid core and reduced soluble concentration. The unloaded nanocarrier was considered safe as indicated by high survival rates (~80%) of Galleria mellonella larvae exposed to the formulation and absence of changes in mammary tissue architecture and inflammatory cell infiltrates after administration in rats. A longer retention of the fluorescent marker in breast tissue was observed after intraductal administration when the NLC was incorporated into the poloxamer gel (65.7±18.9%) compared to its solution (28.2±10.4%) and NLC dispersed in water (30.7±12.1%).