UC DAVIS HEALTH | COMPREHENSIVE CANCER CENTER

25th ANNUAL Cancer Research Symposium

September 19 – 20, 2019

Goodnight Auditorium, Comprehensive Cancer Center

4501 X Street, Sacramento, CA

NCI Designated Comprehensive Cancer Center

25th ANNUAL Cancer Research Symposium

From the Director

I am pleased to welcome you to the UC Davis Comprehensive Cancer Center's 25th Annual Symposium. In its 25th year, this event marks a special milestone for the 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. For the silver anniversary of this event, we organized three sessions: Session I – Population Sciences and Health Disparities, chaired by Dr. Luis Carvajal-Carmona with a component on Cancer Career Development and Training, chaired by Dr. Frederick Meyers; Session II – Basic/Translational Science, chaired by Dr. Kermit Carraway; and Session III – Clinical Research, chaired by Dr. Karen Kelly. As before, we continue to have two poster sessions with prizes, which enable junior and senior scientists to highlight their research while rewarding innovative science.

New to our traditional format this year, the keynote address on Cancer Career Development and Training brings an additional renowned scientist to our campus to share expertise in advancing the next generation of cancer researchers. As we establish our new Office of Education, Training and Workforce Development and increase our educational efforts, I hope this presentation will enlighten us and provide insights on cancer education needs and new advances.

In addition to our guest speakers, we are also highlighting new cutting-edge cancer research from within UC Davis. For twenty-five years this event has allowed us to introduce new faculty, feature research by students, and promote programmatic and multidisciplinary interactions. It is my hope that through this event we can continue to promote the very best of our cancer research, especially in the context of our Trans-Center Themes: Cancer Risk Mitigation and Early Detection, Innovative Cancer Models and Technologies, and Precision Therapeutics and Transformative Imaging.

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

Thank you for your continued support.

Sincerely,

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

SYMPOSIUM COMMITTEE MEMBERS

Primo N Lara, MD
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Executive Associate Dean for Cancer Programs
Professor, Division of Hematology and Oncology, Department of Internal Medicine
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Co-Leader, Population Sciences and Health Disparities Program
Director, Latinos United for Cancer Health Advancement (LUCHA) Initiative
Associate Professor, Department of Biochemistry and Molecular Medicine

Frederick J Meyers, MD, MACP
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Director, Center for Precision Medicine and Data Sciences
Professor, Division of Hematology and Oncology, Department of Internal Medicine

Kermit Carraway, PhD
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Professor, Department of Internal Medicine, Department of Biochemistry and Molecular Medicine

Karen Kelly, MD
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AGENDA

Thursday, September 19, 2019

SESSION I: Population Sciences and Health Disparities

Chair: Luis Carvajal-Carmona, PhD

Time	Title	Presenter	Location
8:00-8:30 am	**Continental breakfast**		**Goodnight Auditorium**
8:30–8:40 am	Introduction and Welcome	**Primo Lara, MD** Director, UCD Comprehensive Cancer Center	
8:40-9:10 am	Keynote Presentation: "Epigenetic Regulators of Prostate and Breast Cancers in African Americans"	**Clayton Yates, PhD** Professor, Department of Biology and Center for Cancer Research Tuskegee University	
9:10-9:25 am	Q&A		
9:25–9:40 am	"Preclinical Evaluation of a Ketogenic Diet in Pancreatic Cancer"	**Gerardo Mackenzie, PhD** Associate Professor, Department of Nutrition, UC Davis	
9:40-9:45 am	Q&A		
9:45–10:00 am	"Impact of Specialized Cancer Centers on Survival Among Children, Adolescents and Young Adults with Acute Lymphoblastic Leukemia (ALL)"	**Elysia Alvarez, MD, MPH** Assistant Professor, Department of Pediatrics, UC Davis	
10:00–10:05 am	Q&A		
10:05–10:15 am	**Break**		
10:15–10:30 am	"Inpatients Costs of Cancer Treatment Among Children and Young Adults with Acute Lymphoblastic Leukemia (ALL) Treated at Specialized Cancer Centers in California"	**Theresa Keegan, PhD, MS** Associate Professor, Division of Hematology and Oncology, UC Davis	
10:30–10:35 am	Q&A		
10:35–10:50 am	"Urban-Rural Variations in Quality of Care and Survival Among Cancer Patients in California"	**Arti Parikh-Patel, PhD, MPH** Program Director, California Cancer Reporting and Epidemiologic Surveillance (CalCARES) Program	
10:50–10:55 am	Q&A		
10:55–11:10 am	"Eliminating Hepatitis B-linked Liver Cancer Disparities: The Contributions of UC Davis Research and Community/Clinical Partnerships"	**Moon Chen Jr., PhD, MPH** Associate Director for Population Sciences and Community Outreach/Engagement, UCD Comprehensive Cancer Center	
11:10–11:15 am	Q&A		

Cancer Career Development and Training

Chair: Frederick Meyers, MD, MACP

Time	Title	Presenter	Location
11:15-11:45 am	Keynote Presentation: "The Importance of Education in a Cancer Center"	**Joanne Mortimer, MD, FACP, FASCO** Vice Chair and Professor, Department of Medical Oncology & Therapeutics Research, Associate Director for Education and Training, City of Hope Comprehensive Cancer Center	**Goodnight Auditorium**
11:45-12:00 pm	Q&A		
12:00–1:30 pm	**Poster Session and Lunch**	**All**	**Cancer Center Breakout Rooms**

SESSION II: Basic/Translational Science

Chair: Kermit Carraway, PhD

Time	Title	Presenter	Location
1:30-2:00 pm	Keynote Presentation: "Collective Mechanisms for Breast Cancer Dissemination and Metastasis"	**Kevin Cheung, MD** Assistant Professor, Division of Medical Oncology, University of Washington, Assistant Member, Fred Hutchinson Cancer Research Center	**Goodnight Auditorium**
2:00–2:15 pm	Q&A		
2:15-2:30 pm	"Targeting Therapy-Resistant Breast Cancer Cells via Lysosomal Cell Death"	**Kermit Carraway, PhD** Professor, Department of Biochemistry and Molecular Medicine, UC Davis	
2:30-2:35 pm	Q&A		
2:35–2:50 pm	"Cell Penetrating Transformable Peptide Nanoparticles for Lysosomal Disruption and Cisplatin Sensitization in Non-Small Cell Lung Cancer"	**Christopher Baehr, BS** PhD Candidate, Department of Biomedical Engineering, UC Davis	
2:50–2:55 pm	Q&A		
2:55-3:05 pm	**Break**		
3:05–3:20 pm	"New Strategies to Target Autophagy for Cancer Therapy"	**Yuanpei Li, PhD** Associate Professor, Department of Biochemistry and Molecular Medicine, UC Davis	
3:20–3:25 pm	Q&A		
3:25–3:40 pm	"Building 3D in vitro Models of the Tumor Microenvironment"	**Steven George, MD, PhD** Chair and Professor, Department of Biomedical Engineering, UC Davis	
3:40–3:45 pm	Q&A		
3:45–4:00 pm	"Molecular Dissection of Wnt5a-Ror Signaling in Development and Cancer"	**Henry Ho, PhD** Associate Professor, Department of Cell Biology and Human Anatomy, UC Davis	
4:00–4:05 pm	Q&A		
End of Day 1			

Friday, September 20, 2019

Time	Title	Presenter	Location
8:00–9:30 am	**Poster Session and Continental Breakfast**	**All**	**Cancer Center Breakout Rooms**
SESSION III: Clinical Research *Chair: Karen Kelly, MD*			
9:30–10:00 am	**David R. Gandara Lectureship on Developmental Therapeutics:** "Anticancer Drug Development: Past, Present and Future"	**Shivaani Kummar, MD, FACP** Professor of Medicine and of Radiology, Associate Division Chief, Medical Oncology Director, Phase I Clinical Research, Stanford Cancer Institute	**Goodnight Auditorium**
10:00–10:15 am	Q&A		
10:15–10:30 am	"Targeting Tumor-Induced Immunosuppression in Glioblastoma."	**Orin Bloch, MD, FAANS** Associate Professor, Department of Neurological Surgery, UC Davis	
10:30–10:35 am	Q&A		
10:35–10:50 am	**Break**		
10:50–11:05 am	"Multi-Species Evaluation of NK Function and Exhaustion Phenotype"	**Robert Canter, MD** Professor, Division of Surgical Oncology, UC Davis	
11:05–11:10 am	Q&A		
11:10–11:25 am	"Development of a Phenotypically Diverse Human Sarcoma Pre-Clinical Disease Model"	**Janai Carr-Ascher, MD, PhD** Assistant Professor, Division of Hematology and Oncology, UC Davis	
11:25–11:30 am	Q&A		
11:30–11:45 pm	Closing Remarks and Poster Awards Announcement	**Primo Lara, MD** Director, UCD Comprehensive Cancer Center	
Symposium Close			

ORAL PRESENTATIONS

Goodnight Auditorium, UC Davis Comprehensive Cancer Center

4501 X Street, Sacramento, CA

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

Clayton Yates, PhD

Professor, Department of Biology and Center for Cancer Research,
Director of Center for Biomedical Research, Tuskegee University

Dr. Clayton Yates is an internationally recognized expert in prostate cancer health disparities research, cell biology, molecular biology, and molecular pathology. Dr. Yates earned his PhD from the University of Pittsburgh School of Medicine Department of Pathology in 2005 as well as certificate of training in Tissue Engineering and Regenerative medicine from the McGowan Institute of Regenerative Medicine. He then went on to complete a postdoctoral fellowship at Emory University School of Medicine Department of Urology. After completing his post-doctoral training in 2007, Dr. Yates accepted a tenure track Assistant Professor position at Tuskegee University in the Department of Biology and Center for Cancer Research. Dr. Yates was promoted to Associate Professor in 2010 and Full Professor in 2014. Dr. Clayton Yates currents holds appoints in the Center for Cancer Research, and a joint appointment Materials Science and Engineering at Tuskegee University. He is also Adjunct faculty at Clark Atlanta University Department of Biology and Department of Pathology at University of Alabama at Birmingham. Dr. Yates has an interest prostate and breast cancer research, particularly in African Americans. Dr. Yates has established several cell lines based models derived from African American patients that are used by many labs today to study molecular events the lead prostate cancer development and metastasis. Additionally, Dr. Yates has identified multiple biomarkers for the prediction of aggressive cancers in African Americans with prostate or breast cancer, and this has led to the development of a novel therapeutic for African American Breast, Prostate, and Pancreatic patients that is posed to enter clinical trials in 2020. Dr. Yates has spoken at over 35 universities and conferences including the 1st NCI Health Disparities Conference and the AACR Distinguished Lecture. Dr. Yates has also received numerous research honors and awards, authored over 65 peer-reviewed publications, member of the editorial board of Scientific Reports. He has received numerous DOD and R level NIH grants in prostate and breast cancer health disparities, totaling over 25 million dollars in extramural funding. Dr. Yates is currently the Co-Director for the Transatlantic Prostate Cancer Consortium, which is focused on understanding the tumor biology in native African men in Nigeria and developing novel clinical interventions for this population. Dr. Yates is currently the principle investigator (PI) of the Research Centers at Minority Institutions (RCMI), site PI of CTSA (jointly with UAB-hub institution), and co-PI of U54 Cancer Health Disparities with Morehouse School of Medicinal and University of Alabama at Birmingham.

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

Joanne Mortimer, MD, FACP, FASCO

Director, Women's Cancers Program
Vice Chair Medical Oncology
Professor, Division of Medical Oncology & Experimental Therapeutics
Associate Director for Education and Training
Baum Family Professor of Women's Cancers
City of Hope Comprehensive Cancer Center

Joanne Mortimer, M.D., F.A.C.P. is the Vice Chair and Professor of the Department of Medical Oncology at the City of Hope and the Director of the Women's Cancers Program. Dr. Mortimer has participated in clinical trials in breast cancer for over 25 years. Her research has focused on assessing the effects of systemic therapies on cancer and normal tissues. Many of these trials have utilized functional imaging and other biomarkers. She is studying the impact of toxicity on breast cancer disease outcome and quality of life. She and her colleagues were the first to report favorable cancer outcomes for women treated with tamoxifen who experience hot flashes.

Dr. Mortimer received her medical degree from the Stritch College of Medicine at Loyola University and completed her internal medicine residency and an oncology fellowship at the Cleveland Clinic Foundation. Previously, Dr. Mortimer was the Deputy Director of Medical Oncology at the Moores Cancer Center at the University of California, San Diego, medical director of the Sentara Cancer Institute; head of hematology and medical oncology and professor of internal medicine at the Eastern Virginia Medical School; director of clinical oncology and professor of medicine at the Washington University School of Medicine in St. Louis, Mo.; associate of clinical research at the Fred Hutchison Cancer Center in Seattle and assistant professor at the University of Washington's School of Medicine.

Dr. Mortimer has served as a member of Oncologic Drug Advisory Committee of the U.S. Food and Drug Administration and continues as a Special Government Employee.

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

Kevin Cheung, MD

Assistant Professor, Division of Medical Oncology
University of Washington
Assistant Member, Fred Hutchinson Cancer Research Center

Dr. Cheung is a cell biologist and medical oncologist dedicated to making discoveries in the laboratory to better detect, prevent and treat metastatic breast cancer. Dr. Cheung graduated from Cornell medical school, completed his internal medicine residency training at the Brigham and Women's Hospital and medical oncology fellowship training at Johns Hopkins where he conducted postdoctoral research with Andy Ewald. Dr. Cheung is currently an Assistant Member in the Translational Research Program, at the Fred Hutchinson Cancer Research Center, and cares for breast cancer patients at the Seattle Cancer Care Alliance.

KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

David R. Gandara Lectureship on Development Therapeutics

Shivaani Kummar, MD, FACP

Professor of Medicine and Radiology,
Co-Director, Translational Oncology Program at Stanford,
Director of the Phase I Clinical Research Program, Stanford University

Upon completing her medical degree from Lady Hardinge Medical College in New Delhi, India, Shivaani Kummar moved to the United States to train in Internal Medicine at Emory University in Atlanta, Georgia. Following this Kummar was selected to pursue fellowship training at the National Institute of Health (NIH) in Medical Oncology and Hematology, which culminated in being offered a faculty position at Yale University, New Haven CT. After spending four years as Assistant Professor of Medicine at Yale Cancer Center, she moved back to the National Cancer Institute (NCI), NIH, where she developed a clinical research program in novel cancer therapeutics. In 2011 she became Head of Early Clinical Trials Development in the Office of the Director, Division of Cancer Treatment and Diagnosis, NCI. Kummar moved to Stanford University in 2015 as Professor of Medicine and Director of the Phase I Clinical Research Program. Kummar's research interests focus on developing novel therapies for cancer. She specializes in conducting pharmacokinetic and pharmacodynamic driven first-in-human trials tailored to make early, informed decisions regarding the suitability of novel molecular agents for further clinical investigation. Kummar is the principal investigator of numerous early phase trials, and serves on multiple national and international scientific committees.

ABSTRACTS OF ORAL PRESENTATIONS (THURSDAY)

SESSION I: Populations Sciences and Health Disparities

Chair: Luis Carvajal-Carmona, PhD

KEYNOTE LECTURE: EPIGENETIC REGULATORS OF PROSTRATE AND BREAST CANCERS IN AFRICAN AMERICANS

Clayton Yates, PhD, Professor, Department of Biology and Center for Cancer Research, Tuskegee University

[Abstract Not Available]

PRECLINICAL EVALUATION OF A KETOGENIC DIET IN PANCREATIC CANCER

Natalia E Cortez Penso[1], Brian V Hong[1], Emily M. Villarreal[1], Jon J Ramsey[2], Gerardo G Mackenzie, PhD[1,3]

[1]Department of Nutrition, University of California, Davis, CA
[2]Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA
[3]University of California, Davis Comprehensive Cancer Center, Sacramento, CA

Pancreatic ductal adenocarcinoma (PDA) is a deadly cancer characterized by the rapid decline in patients' quality of life. More than 80% of patients with pancreatic ductal adenocarcinoma (PDA) suffer from cachexia and up to 20% die directly from it. Thus, there is an urgent need for new strategies to combat this disease; and the exploration of dietary interventions is a critical component. Among various dietary interventions, the ketogenic diet (KD) has been gaining attention for its anti-tumor, anti-inflammatory potential. In a recent study, we have shown that a KD significantly increases mouse median lifespan and survival, compared to mice fed a control diet. Importantly in these aged mice, only those consuming a KD display preservation of physiological function, including motor function. However, its effect in cancer remains elusive. Thus, our objective was to determine whether a KD mitigates cachexia and/or increases survival in a clinically relevant genetically engineered *LSL-Kras$^{G12D/+}$; LSL-Trp53$^{R172H/+}$; Pdx1-Cre* (KPC) model of PDA. After confirming the presence of a pancreatic tumor by high resolution ultrasound imaging, male and female KPC mice were fed either a control diet (CD; %kcal: 15% protein, 65% carb, 20% fat), or a KD (%kcal: 15% protein, ~1% carb, 84% fat) until an endpoint related to PDA progression was met. Forelimb grip strength, body composition, and non-fasting glucose and ketone levels were evaluated at baseline, monthly and at time of sacrifice. As expected, mice fed a KD had higher levels of ketone bodies in blood, compared to CD. Even though, the KD did not significant extend KPC mice survival, KPC mice fed a KD outperformed the KPC mice fed CD in the grip strength test at 2 months on the diets. Moreover, gastrocnemius weight was significantly higher in mice fed a KD compared to mice fed a CD. When evaluating organ weights at time of euthanasia, the weight of lungs and spleen, but not those of pancreas or liver, were significantly higher in the CD group compared to the KD group. In summary, although no changes in overall survival, a KD maximized and preserved motor function strength in mice bearing PDA progression. Additional studies are underway to determine the mechanisms on how KD improves and preserves muscle strength in PDA, as well as to evaluate its effect in combination with chemotherapy.

Acknowledgements: Funded in part by Startup funds and UCDCCC-ELEMENTS award to GGM. Jastro and UC-MEXUS fellowship to NEC.

IMPACT OF SPECIALIZED CANCER CENTERS ON SURVIVAL AMONG CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Elysia M Alvarez, MD, MPH,[1] Marcio Malogolowkin,[1] Jeffrey S. Hoch,[2] Qian Li,[3] Ann Brunson,[3] Brad H Pollock,[2] Lori Muffly,[4] Ted Wun,[3,6] Theresa HM Keegan[2.3]

[1]Division of Pediatric Hematology and Oncology, University of California, Davis School of Medicine

[2]Division of Health Policy and Management, Department of Public Health Sciences, University of California Davis School of Medicine, Sacramento, CA
[3]Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA
[4]Division of Bone Marrow and Transplantation, Stanford University, Stanford, CA
[6]University of California, Davis Clinical and Translational Science Center

Background: We previously demonstrated that adolescent and young adult (AYA) patients who received induction treatment at specialized cancer centers (SCC; versus community hospitals) had lower early mortality within 60 days of diagnosis. However, the effect of location of treatment on long term survival has not yet been evaluated at the population-level.

Methods: Using the California Cancer Registry linked to a statewide hospitalization database, we identified children (0-18 years) and AYAs (19-39 years) with first primary ALL who received inpatient treatment, 1991-2014 (n = 7,724). Patients were classified as receiving all or part/none of their treatment at a SCC (Children's Oncology Group or National Cancer Institute-designated cancer center) within 3 years of diagnosis. Propensity scores were created for treatment at an SCC in each age-group. Inverse probability-weighted, multivariable Cox regression models estimated the associations between location of treatment, sociodemographic and clinical factors with leukemia-specific and overall survival. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CI).

Results: Overall, 21.3% of children and 42.6% of AYAs died over the study period (median follow-up time: 11.6 years). Seventy-eight percent (n = 4511) of children and 19% of AYAs (n = 356) received all their treatment at SCCs. Receiving all treatment at a SCC was associated with superior leukemia-specific (hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.67-0.88) and overall survival (HR 0.87, CI 0.77-0.97) in children and in YAs (HR 0.71, CI 0.61-0.83; HR 0.70, CI 0.62-0.80) even after controlling for complications. In both age groups, worse survival was associated with older age, Hispanic and African American race/ethnicity (vs non-Hispanic white), public insurance (vs private) and comorbidities.

Conclusions**:** Our results demonstrate that treatment at a SCC through end of therapy is associated with better leukemia-specific survival in children and AYAs. In contrast to AYAs, the majority of children receive care at a SCC, but both age groups benefit from care at a SCC. This highlights the need for these patients to be referred to and treated at SCCs.

INPATIENTS COSTS OF CANCER TREATMENT AMONG CHILDREN AND YOUNG ADULTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TREATED AT SPECIALIZED CANCER CENTERS IN CALIFORNIA

Theresa HM Keegan, PhD, MS,[1] Elysia Alvarez,[2] Qian Li,[1] Ann Brunson,[1] Ted Wun,[1] Jeffrey S Hoch[3]

[1]Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, Department of Internal Medicine, University of California Davis School of Medicine, Sacramento, CA
[2]Division of Pediatric Hematology and Oncology, Department of Pediatrics, University of California Davis School of Medicine, Sacramento, CA
[3]Division of Health Policy and Management, Department of Public Health Sciences, University of California Davis School of Medicine, Davis, CA

Introduction: We previously demonstrated that receiving all cancer treatment at specialized cancer centers (SCCs; versus community hospitals) through end of therapy is associated with better leukemia-specific survival in children (0-18 years) and young adults (YA; 19-39 years) diagnosed with ALL in California. While both age groups benefit from care at a SCC, we found only a minority of YAs (36%), compared with children (84%), received care at a SCC. Our prior findings highlight the need for these patients to be referred to and treated at

SCCs, but there are potential cost differences associated with this recommendation that have not been previously examined.

Methods: Using the California Cancer Registry linked to the Office of Statewide Health and Planning and Development (OSHPD) statewide hospitalization database, we identified children and YAs (19-39 years) with first primary ALL who received inpatient treatment from 1995-2014 and had at least 3 years of follow-up. Patients were classified as receiving all or part/none of their treatment at a SCC (Children's Oncology Group or National Cancer Institute-designated cancer centers for children and National Cancer Institute-designated cancer centers for YAs) within 3 years of diagnosis to capture the full time of potential primary treatment. Total charges for each admission and hospital level financial information were used to calculate costs (adjusted for inflation to 2016 US dollars) for each admission, excluding peri-partum admissions and those associated with traumatic accidents. One large health maintenance organization system in California did not report charges to OSHPD and was excluded from the analysis (13% of the patient population). In addition, patients needed to have at least 80% of charge data to be included in the primary analysis, resulting in a study population of 5,167 ALL patients. We determined the number of inpatient days and cumulative inpatient costs within 3 years of diagnosis. Mean and median costs overall and per day by age group and location of care were compared using t-tests and Kruskal Wallace tests. We conducted sensitivity analyses 1) limiting our analyses to only patients with all charge data available (n=5,118) and 2) excluding patients with stem cell transplant (n=693) to determine the impact of these factors on study findings.

Results: The mean cost for children receiving all care at SCCs vs non-SCCs was $216,439 (median=$121,039) vs $191,082 (median=$84,529) (p mean = 0.008; p median = <0.001). The cost per day was higher at SCCs (mean=$2,840; median=$2,529) than non-SCCs (mean=$2,283; median=$1,865) (p mean < 0.001; p median < 0.001). In children, the mean number of inpatient days within 3 years of diagnosis was similar for those who did (n=70 days) and did not (72 days) receive all cancer care in SCCs (p=0.70). Among YAs, the mean cost for patients receiving all treatment at SCCs was $380,556 (median=$308,864) vs $346,706 (median=$241,847) at non-SCCs (p mean=0.02; p median < 0.001). The cost per day was higher at SCCs (mean=$3,730; median=$3,537) than non-SCCs (mean=$3,224; median=$2,917) (p mean < 0.001; p median < 0.001). YAs receiving all cancer care at SCCs (99 days) had a similar mean number of inpatient days to those receiving care at non-SCCs (101 days) (p=0.97). In the sensitivity analyses excluding patients receiving a transplant, the mean cost was lower at both SCCs and non-SCCs, but the differences in costs in children and YAs by location of care remained. In addition, results were similar when analyses were limited to patients with complete charge data.

Conclusion: In this large, population-based cohort of pediatric and YA patients with ALL, we found that inpatient costs and number of inpatient days were higher among YAs than children with ALL. In addition, in each age group, the costs of inpatient care during the full course of therapy for primary ALL was higher in patients receiving all of their care at SCCs compared patients receiving part or none of their care at an SCC. As inpatient costs do not reflect the total burden associated with cancer care, future studies should consider how location of care impacts outpatient, emergency department and out-of-pocket costs. Given findings of better outcomes among children and YAs receiving all care at SCCs

URBAN-RURAL VARIATIONS IN QUALITY OF CARE AND SURVIVAL AMONG CANCER PATIENTS IN CALIFORNIA

Arti Parikh-Patel[1] PhD, MPH, Cyllene R Morris[1], Kenneth W Kizer[1,2], Theresa Keegan[1,3]

[1]California Cancer Reporting and Epidemiologic Surveillance (CalCARES) Program, Institute for Population Health Improvement, University of California Davis Health
[2]University of California, Davis School of Medicine, and Betty Irene Moore School of Nursing
[3]Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA

Background: Although more urbanized than the nation as a whole, California has a significant rural land mass, with rural communities spread throughout multiple counties Previous research on the impact of rural place of residence on cancer treatment and outcomes has yielded inconsistent results. Access to care, socioeconomic status (SES), race/ethnicity and other factors may obscure the relationship between rurality and cancer

treatment and outcomes. This study sought to determine the independent effect of rural place of residence on the quality and outcomes of cancer care statewide.

Methods: Persons diagnosed with breast, ovarian, endometrial, cervix, colon, lung, or gastric cancer between 2004 and 2017, inclusive, were identified in the California Cancer Registry. Medical Service Study Areas (MSSA), a census tract based, state-specific geographic unit of analysis, were used to classification areas as urban or rural. Multivariate logistic regression and Cox proportional hazards models were generated to assess the independent effect of area of residence on quality of care and survival, adjusting for health insurance, age, sex, race/ethnicity, comorbidity, SES, and facility type. Quality of cancer treatment was evaluated using established Commission on Cancer quality measures.

Results: A total of 987,458 cancer patients were evaluated, with 14% classified as living in a rural area. Rural cancer patients were significantly older, non-Hispanic white, and of lower SES compared to urban residents. Rural area patients were significantly less likely to undergo radiation after breast conserving surgery (O.R: 0.90, 95% C.I: 0.85, 0.95). Both colon (O.R: 0.83, 95% C.I: 0.75, 0.91) and gastric (O.R: 0.83, 95% C.I: 0.72, 0.95) cancer patients had significantly lower odds of having the recommended number of lymph nodes surgically removed and examined. For all cancers, survival was similar in urban and rural groups.

Conclusions: Rurality is an independent predictor of receiving recommended radiation treatment and surgery for some cancer types. Despite differences in quality of care, controlling for demographic factors and health insurance attenuated this relationship, and eliminated survival differences between urban and rural cancer patient populations in California. Further research into the individual and structural factors underlying the association between rurality and receipt of recommended treatment is warranted.

ELIMINATING HEPATITIS B-LINKED LIVER CANCER DISPARITIES: THE CONTRIBUTIONS OF UC DAVIS RESEARCH AND COMMUNITY/CLINICAL PARTNERSHIPS

Moon Chen Jr., PhD, MPH, Division of Hematology and Oncology, UCD Comprehensive Cancer Center

Only one disease in human history has ever been eliminated such that no disparities in the incidence or mortality rates exist for any group. That disease, eradicated in 1979, is smallpox. We hypothesize that by applying the same principles, that eliminating disparities due to Hepatitis B (HBV)-linked liver cancer is an attainable aspiration. This presentation highlights the achievements that the UC Davis-led research has made and the activities that are being conducted to contribute to the elimination of HBV-linked liver cancer.

Aspiration: Just as was smallpox in its day, liver cancer (hepatocellular carcinoma or HCC) in our day is a leading global cause of morbidity and mortality. Liver cancer is the world's second deadliest cancer and leads all cancer organ sites in annual percentage increases in the U.S. In California and in our catchment area, liver cancer is the third leading cause of cancer mortality for Hispanics and Asian Pacific Islanders who together comprise more than half of California's population. Like smallpox, HBV is screen-able and vaccine-preventable. HCC is etiologically attributable to viral, lifestyle, and metabolic factors, but HBV is the most common global risk factor for HCC. As with smallpox, screening to detect HBV is foundational and vaccination against HBV is pivotal to disease prevention.

Achievements: UC Davis was first funded for research to mitigate the burden of HBV by the National Cancer Institute (NCI) and the National Institute on Minority Health and Health Disparities (NIMHD) in 2006. Our team published the most extensive epidemiological analyses that documented that Asian Americans and specifically, the Hmong have the highest mortality rates and lowest survival rates for HCC. We determined that HCC among could be attributed to their highest HBV prevalence rates among all California Asian groups as well as their potentially heightened genetic predisposition due to a single nucleotide polymorphism in the PNLPA3 gene. To mitigate this burden, our NIH-funded research documented that bilingual/bicultural Hmong lay health educators achieved both statistically significant and programmatic effective increases in serological testing for HBV in a community-based, randomized controlled group design. Our CDC-funded studies demonstrated that both in-reach (within UCD Health) and outreach (community) are complementary strategies to identify those at risk and link them to care. We developed an EMR-alert to identify at-risk UCD patients who had not been screened for HBV and over the years screened more than 5300 Asian Americans for HBV.

Activities: These cumulative accomplishments laid the foundation for the current efforts to train medical assistants at the Health and Life Organization (HALO) Federally Qualified Health Center-Look-Alike to serve as intervention agents to mitigate the cancer burden among patients. UC Davis is leading an ongoing community/clinical collaboration that encompasses the perinatal period throughout the lifespan. Among the realities we are rectifying is enhancing HALO's electronic medical record system. Using the enhanced EMR we will be able to assure that all HALO pregnant patients who are perinatally infected with HBV are treated and their newborns are vaccinated promptly. By assuring that all under age 19 are vaccinated against HBV and adults screened and linked to care, we aim to spare the next generation of Sacramento residents from HBV-linked HCC.

Conclusions: Applying the principles of smallpox eradication appears to be a reasonable blueprint to follow to eliminate HBV-linked HCC. "The longest journey begins with a single step."

Acknowledgments: UC Davis colleagues who have been instrumental in the mitigation of HBV-linked HCC research include: CL Bowlus, MD; EW Chak, MD, MPH; JHT Dang, PhD, MPH; RJ Jan, MD; D LeTran, BS; ST MacDonald, MD, MP Pauly, MD; SL Stewart, Ph.D., CG Tepper, PhD; and GT Yang, BS. We are grateful to partnering with the California Primary Care Association; Health and Life Organization; Hmong Women's Heritage Association; Paul Hom Asian Clinic; Sacramento County Public Health; Shalom Cancer Support Group; and the Vietnamese Cancer Awareness & Research Society. This research effort has been supported by the NCI; NIMHD; CDC; Bristol-Meyers Squibb Foundation; Francis Yee Fund for Cancer Disparities Research; and the Office of Minority Health/U.S. Department of Health and Human Services.

Cancer Career Development and Training

Chair: Frederick Meyers, MD, MACP

KEYNOTE LECTURE: THE IMPORTANCE OF EDUCATION IN A CANCER CENTER

Joanne Mortimer, MD, Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center

[No Abstract Available]

SESSION II: Basic/Translational Science

Chair: Kermit Carraway, PhD

KEYNOTE LECTURE: COLLECTIVE MECHANISMS FOR BREAST CANCER DISSEMINATION AND METASTASIS

Kevin Cheung, MD, Division of Medical Oncology, University of Washington, Fred Hutchinson Cancer Research Center

An essential step for metastasis is the dissemination of tumor cells into the systemic circulation. Although this process has been conceptualized as the dissemination of individual tumor cells to distant organs, increasing clinical and experimental evidence indicate that tumor cells invade, circulate, and extravasate as multicellular clusters. A key question arising from these findings is how mechanistically clusters of cancer cells have superior metastasis forming potential. Here we unveil the molecular signaling pathways robustly induced by clustering of breast tumors and show how the three-dimensional architecture of tumor cell clusters shapes their signaling output. We functionally dissect cluster-based signaling and discuss the implications of our findings for theories of cancer metastasis and for therapeutically targeting metastatic breast cancer.

TARGETING THERAPY-RESISTANT BREAST CANCER CELLS VIA LYSOSOMAL CELL DEATH

Kermit Carraway, PhD[1], Anastasia Berg[1], Michelle Hu[1], Ashley Rowson-Hodel[1], Megan Showalter[2], Oliver Fiehn[2], Jenny Chen[1]

[1]Department of Biochemistry and Molecular Medicine, and UC Davis Comprehensive Cancer Center, UC Davis School of Medicine, Sacramento, CA 95817
[2]Department of Molecular and Cellular Biology, and West Coast Metabolomics Center, UC Davis College of Biological Sciences, Davis, CA 95616

Therapeutic resistance leading to cancer recurrence poses a difficult barrier to long-term patient survival in clinical disease management. Cellular resistance to apoptosis is perhaps the most critical factor conferring therapeutic failure to both conventional chemotherapeutic and targeted agents. Tumors frequently activate anti-apoptotic cell survival pathways in response to apoptosis-inducing drugs, and can acquire genetic mutations in early stages of tumor development that cause caspase-dependent cell death pathways to malfunction. Consequently, apoptosis-resistant tumor cell subsets can persist after treatment to seed tumor recurrence and metastasis, even in cases of apparent complete clinical response. We are examining the possibility that therapy-resistant breast tumor cell populations may be targeted by engaging the programmed necrotic lysosomal cell death (LCD) mechanism by a derivative of the FDA-approved drug amiloride. This agent, hexamethylene amiloride (HMA), kills breast tumor cells by a caspase- and autophagy-independent mechanism, and acts equally efficiently toward cell lines representing the major immunohistochemically-defined breast cancer subtypes. HMA does not act on non-transformed mammary epithelial cells or primary normal cells derived from a variety of tissues. Importantly, HMA acts toward cancer stem cell (CSC)-like subpopulations and persister cells that remain after treatment with chemotherapeutics. The tumor cell-specific cytotoxic mechanism appears to involve the induction of lysosomal membrane permeabilization (LMP), which releases lysosomal contents into the cytosol to trigger the LCD mechanism. The demonstration that HMA and other lysosomotropic agents can eradicate therapy-resistant tumor cell populations *in vitro* and *in vivo* will pave the way for the development of novel classes of drugs that can induce LMP to specifically elicit lysosomal cell death in breast and other tumor cells.

The studies are supported by the CCSG Institutional Research Grant Pilot Funding Program

CELL PENETRATING TRANSFORMABLE PEPTIDE NANOPARTICLES FOR LYSOSOMAL DISRUPTION AND CISPLATIN SENSITIZATION IN NON-SMALL CELL LUNG CANCER

Christopher M Baehr, PhD Candidate, Lu Zhang, Lei Wang, Kit S Lam

Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, UC Davis NCI-Designated Comprehensive Cancer Center, Sacramento, CA 95817, USA

In the United States, non-small cell lung cancer (NSCLC) accounts for approximately 14% of all cancer deaths and is by far the largest contributor to cancer deaths annually. Despite the advances in check point blockade

immunotherapy, only about 35% of patients respond to treatment. Traditional combination chemotherapies are toxic and resistances to platinum-based chemotherapies are frequently developed. Therefore, novel mechanisms by which to induce cancer cell death and chemotherapeutic sensitization are highly sought after. Recently, several drug candidates (e.g. Salinomycin, Oleocanthal, hexamethylene amiloride) have been shown to selectively induce lysosomal membrane permeabilization (LMP) in aggressive cancer lines. Others like chloroquine, an anti-malarial drug, have been shown to sensitize NSCLCs to cisplatin in human trials. These drugs and others have led to great interest in LMP and lysosome dysregulation as a cancer therapeutic target. However, novel approaches are needed to overcome the two central limitations of current lysosomal inhibitors and LMP agents: low specificity potency. Here, we have developed amyloid beta mimetic peptide amphiphiles which self-assemble into nanoparticles at physiological pH but form high aspect ratio nanofibers in acidic pH (< pH5). These nanoparticles are decorated with a cell penetrating peptide which induces endocytosis and colocalization of the material with the lysosome (Persons coefficient: 0.94). The acidity of the lysosome induces the formation of amyloid fibrils which cause LMP and cell death. We show that these transformable peptide nanoparticles are highly toxic to A549 cells with an IC50 in the low micromolar range and sensitize A549 cells to cisplatin in the nanomolar range. Moreover, while these fibrils form in A549 lung carcinoma cells, they do not form in HEK 293, 3T3 fibroblasts or human cerebral microvascular endothelial cells. This is the first example of lysosome induced molecular self-assembly and it offers a promising new strategy for cancer therapy.

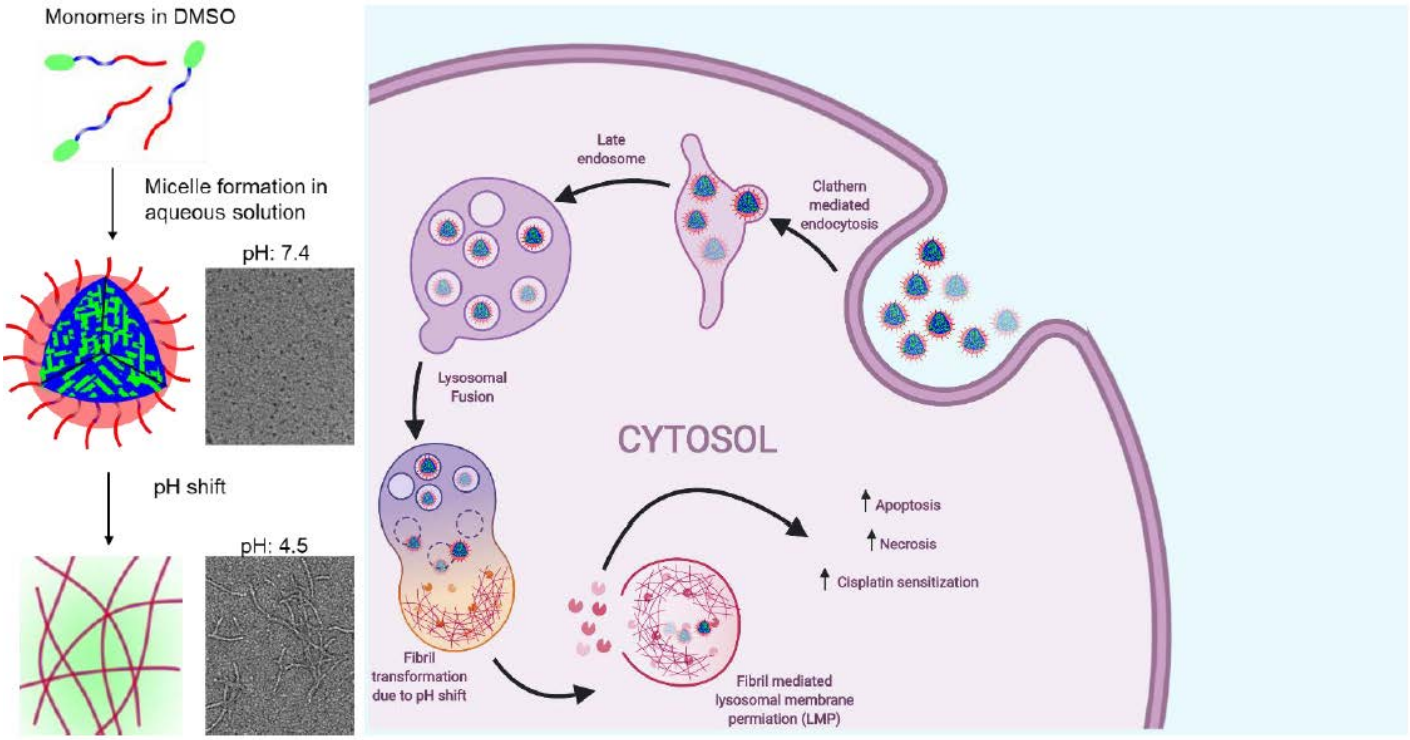

Figure 1: Schematic of Cell penetrating transformable peptide nanoparticle (CPTNP) action *in vitro*. CPTNPS form nanoparticles at physiological pH and nanofibers in acidic pH. CPTNPs are endocytosed by cells and trafficked to the lysosome. Lysosomal pH shift induces nanofibril formation and lysosomal membrane permeation, thereby releasing the lysosomal contents into the cytoplasm and inducing LMP mediated cell death and cisplatin sensitization.

NEW STRATEGIES TO TARGET AUTOPHAGY FOR CANCER THERAPY

Zhao Ma[1], Dalin Zhang[1], Mythili Ramachandran[1], Tzu-yin Lin[2], Yuanpei Li, PhD[1]

[1]Department of Biochemistry and Molecular Medicine
[2] Department of Internal Medicine
UC Davis Comprehensive Cancer Center
University of California, Davis

Autophagy, a catabolic process which harnesses lysosomal-mediated degradation of cellular proteins and organelles to regenerate energy in the setting of metabolic stress, is associated with drug resistance to a variety of cancers. Autophagy in the tumor microenvironment activates several tumor escape mechanisms,

which effectively counteract anti-tumor immune responses mediated by natural killer and cytotoxic T lymphocytes. Therefore, strategies aiming at targeting autophagy in cancer cells in combination with other therapeutic strategies have inspired significant interest to promote tumor regression and overcome immunological tolerance. Autophagy inhibition decreases ERK phosphorylation and synergizes MEK5 as well as ERK inhibitors for highly effective cancer treatments. Furthermore, targeting autophagy inhibits tumor growth by enhancing NK cells infiltration. In preclinical models, autophagy inhibition with chloroquine (CQ) derivatives augments the efficacy of many anticancer therapies, but CQ has limited activity as a single agent. Clinical trials are underway combining anticancer agents with hydroxychloroquine (HCQ), but concentrations of HCQ required to inhibit autophagy are not consistently achievable in the clinic. New strategy to target autophagy for cancer therapy is needed.

BUILDING 3D IN VITRO MODELS OF THE TUMOR MICROENVIRONMENT

Steven George, MD, PhD, Department of Biomedical Engineering, UC Davis

[Abstract Not Available]

MOLECULAR DISSECTION OF WNT5A-ROR SIGNALING IN DEVELOPMENT AND CANCER

Henry Ho, PhD, Department of Cell Biology and Human Anatomy, UC Davis School of Medicine

The Wnt signaling system controls diverse biological processes, and dysfunction of the Wnt signaling system contributes to a wide variety of pathological conditions, including cancer. The role of canonical Wnt/beta-catenin signaling in early phase of cancer progression, such as cancer initiation and proliferation, has been well established. During the past several years, noncanonical, beta-catenin-independent Wnt signaling has emerged as a major player in promoting later stages of cancer progression, such as metastasis. During normal embryonic development, noncanonical Wnt signaling controls cytoskeleton-driven morphogenetic cell behaviors, such as polarization, adhesion and migration, and it appears that cancer cells have hijacked the pathway to augment their metastatic potentials. The molecular mechanisms that govern noncanonical Wnt signaling in both developmental and cancer contexts, however, have remained poorly understood. Our lab has used a combined approach of mouse genetics and protein biochemistry to investigate a noncanonical Wnt signaling pathway involing the prototypic noncanonical Wnt ligand, WNT5A, and its receptor ROR. Our study identified several novel factors in the Wnt5a-Ror pathway and led to the development of new molecular assays for measuring Wnt5a-Ror signaling activity in live cells. It is our hope that this line of investigation will deepen our understanding of the Wnt5a-Ror signaling and help devise novel therapeutic strategies to combat cancer metastasis.

Acknowledgements: This work was made possible by the generous support from the following grants: ACS/IRG (IRG-95-125-13) and NIH/NIGMS (1R35GM119574-01)

ABSTRACTS OF ORAL PRESENTATIONS (FRIDAY)

SESSION III: Clinical Research

Chair: Karen Kelly, MD

KEYNOTE LECTURE: ANTICANCER DRUG DEVELOPMENT: PAST, PRESENT AND FUTURE

Shivaani Kummar, MD, FACP, Departments of Medicine and Radiology, Stanford University

The landscape of early phase trials is rapidly evolving and phase I trials for oncology therapeutics are becoming increasingly complex proof-of-concept clinical trials that may even directly support product registration. During the talk, I will reflect on the history of 'chemotherapy', the evolution of anticancer drug development, and future directions. I will discuss some of the challenges and the promise of 'personalized medicine', and tailoring therapy for one patient at a time.

TARGETING TUMOR-INDUCED IMMUNOSUPPRESSION IN GLIOBLASTOMA

Orin Bloch, MD, FAANS, Department of Neurological Surgery, UC Davis

[Abstract Not Available]

MULTI-SPECIES EVALUATION OF NK FUNCTION AND EXHAUSTION PHENOTYPE

Robert Canter, MD, Division of Surgical Oncology, UC Davis

Despite the well-recognized role of NK cells in cancer immunosurveillance and the application of NK cells to some hematologic malignancies, success in the translation of NK immunotherapy to patients with solid tumors has been limited. Although the concept of T cell exhaustion has emerged as critical to cancer immunotherapy, less is known about the exhaustion of NK cells and whether similar immunoregulatory mechanisms are necessary in shorter-lived, polyclonal NK cells. In this study, our objective was to comprehensively assess PD-1 expression on NK cells using multiple sources and readouts. Primary human tumor samples, ex vivo culturing, mouse tumors and viral models were all assessed using flow cytometry, qRT-PCR and RNA sequencing. We demonstrate that under multiple activating conditions, highly purified human and mouse NK cells consistently lack PD-1 expression despite the marked upregulation of other regulatory markers such as TIGIT. We further show that neither NK cells from T-cell deficient Rag2-/- mice nor from transgenic PD-1 reporter mice express PD-1 using tumor or viral infection models. Asialo-GM1 (ASGM1), was also significantly expressed on activated T cells co-expressing PD-1 contributing to in vivo effects. We also demonstrate that dog NK cells under diverse activating conditions are hallmarked by marked upregulation of multiple activation markers, including NKp46, as well as upregulation of TIGIT with minimal changes in PD-1 and PD-L1. These data have important implications when attempting to discern NK from T cell effects depending on the models used and whether PD-1 blockade will in fact directly impact or augment NK cell therapies.

DEVELOPMENT OF A PHENOTYPICALLY DIVERSE HUMAN SARCOMA PRE-CLINICAL DISEASE MODEL

Janai Carr-Ascher, MD, PhD[1], Lisa Ta[2], Jung Wook Park[3], Donald Johnson[2], Ross Okimoto[3], Owen Witte[2]

[1]University of California, Davis Comprehensive Cancer Center
[2]University of California, Los Angeles Broad Stem Cell Center
[3]Duke University, Department of Pathology
[4]University of California, San Francisco, Division of Hematology/Oncology

The development of novel therapies for sarcoma has been hampered by the considerable heterogeneity of the disease and the limited understanding of the molecular mechanisms driving sarcoma formation and evolution. The current research focuses on the development of a new pre-clinical model for the study of sarcoma using a

primary human transformation system. Mesenchymal stem cells will be transduced with lentivirus that either expresses an oncogene or target a tumor suppressor. Gene combinations will be evaluated for ability to form phenotypically diverse tumors in immunocompromised mice. In addition, a metastatic model using patient derived xenografts will be developed using orthotopic injection and evaluation of lung metastasis. This will allow for a system in which metastatic tumors can be compared to localized growth. The combination of a sarcomagenesis and metastasis model will result in a system that can be used to investigate the development of sarcoma, understand subtype heterogeneity, and function as a tool for the development of novel therapies for our patients.

POSTER PRESENTATIONS

Breakout Rooms, UC Davis Comprehensive Cancer Center

4501 X Street, Sacramento, CA

Poster Index:

Poster Abstracts:

Thursday poster session: 12:00 pm – 1:30 pm
Posters can be put up from 8:00 am
Posters must be taken down by 4:15 pm

Friday poster session: 8:00 am – 9:30 am
Posters can be put up from 7:30 am
Posters must be taken down by 12:30 pm

THURSDAY POSTER PRESENTATIONS (INDEX)

16. **Generating a Cell Based Assay for High Content Screening of Small Molecules and PROTAC Molecules**
Neeki Tahmassebi, Cristabelle De Souza, Harikumara Kathi, Dan Aki, Nina Nelson, Jeremy Chien

17. **Development of Bioluminescent Probes for Visualizing Metal Dynamics in Cancer Biology**
Justin O'Sullivan, Joseph AbouAyash, Adam Hillaire, Marie Heffern

18. **Dominance of Metabolic Control Determines Cancer Subtype-specific Response to Therapeutics of Lipid Metabolism**
Demin Cai, Junjian Wang, Bei Gao, Jin Li, June X. Zou, Hongye Zou, Oliver Fiehn, Hong-Wu Chen

19. **Therapeutic Targeting MDR1 Expression by Rorγ Antagonists Resensitizes Cross-Resistant CRPC to Taxane via Coordinated Induction of Cell Death Programs**
Yongqiang Wang, Zenghong Huang, Christopher Z Chen, Chengfei Liu, Christopher P Evans, Allen C Gao, Hong-Wu Chen

20. **Orally Effective Antagonists of Nuclear Receptor ROR-γ Inhibit CRPC Tumor Growth and Aggressive Programs**
Zenghong Huang, Junjian Wang, Joy C Yang, Jin Li, Eva Corey, Christopher P Evans, Hong-Wu Chen

21. **Characterization of a Novel Androgen Receptor Variant, Vbl-1, in Bladder Cancer**
Kimberley D Katleba, Alan P Lombard, Chris A Lucas, Kristine S Nishida, Han Bit Baek, Paramita M Ghosh, Maria Mudryj

22. **Mitigating EGFR- and ERK-Dependent Resistance to Enzalutamide in Castration-Resistant Prostate Cancer**
Thomas M Steele, Maitreyee K Jathal, Salma Siddiqui, Sisi Qin, XuBao Shi, Clifford G Tepper, Ralph W deVere White, Manish Kohli, Liewei Wang, Allen C Gao, Paramita M Ghosh

23. **Expression of Arginosuccinate Synthase 1 (ASS1) in Localized and Metastatic Prostate Cancer Tissue**
Salma Siddiqui, Leandro S D'Abronzo, Zsofia A Kiss, Blythe P Durbin-Johnson, Rafael E Jimenez, Manish Kohli, Allen C Gao, Hsing-Jien Kung, Paramita M Ghosh

24. **Overcoming ABCB1-Mediated Olaparib Resistance in Advanced Prostate Cancer**
Alan P Lombard, Chengfei Liu, Cameron Armstrong, Wei Lou, Christopher P Evans, Allen C Gao

25. ***Novel Galectin-1 Inhibitor for Castration-Resistant Prostate Cancer***
Zsofia A Kiss, Salma Siddiqui, Sisi Qin, Liewei Wang, Kit S Lam, Tsung-Chieh Shih, Ming Hsiang Hong, Futong Liu, Paramita M Ghosh, Ruiwu Liu

26. **Methionine Adenosyltransferase 1a (MAT1A) Enhances Cell Survival During Chemotherapy Treatment and May Be Associated with Drug Resistance in Bladder Cancer**
Kelly A Martin, Nicholas R Hum, Aimy Sebastian, Salma Siddiqui, Paramita M Ghosh, Chong-xian Pan, Ralph de Vere White, Gabriela G Loots

27. **Characterization of the tumor microenvironment using single cell transcriptomics of triple negative breast cancer allografts treated with doxorubicin**
Nicholas R Hum, Aimy Sebastian, Sean Gilmore, Kelly A Martin, Elizabeth K Wheeler, Matthew A Coleman, Gabriela G Loots

28. **Elucidating the Mechanism of Action for Hexamethylene Amiloride in the Treatment of Breast Cancer**
Michelle Hu, Anastasia Berg, Ashley R Rowson-Hodel, Maddy Wheeler, Jenny Chen, Kermit L Carraway, III

29. **Impact of the Aryl Hydrocarbon Receptor Signaling Pathway on Mammary Tumorigenesis**
Colleen Sweeney, Sarah Kado, Carla Dahlem, Francis He, Gwendal Lazennec, Christoph Vogel

30. **Intratumor Heterogeneity in Gastric Adenocarcinomas from Latinos**
Ted Toal, Guadalupe Polanco Echeverry, Ruta Sahasrabudhe, Mabel Bohorquez, Javier Torres, Shiro Urayama, Amanda Kirane, Magdalena Echeverry, Luis G Carvajal Carmona

31. **Feasibility Study to Identify and Collect Data on Environmental Risk Factors from Hispanic Women Diagnosed with Lung Cancer**
Rosemary D Cress, Amy K Klapheke

32. **Recent Smoking-Attributable Fractions of Cancer Deaths and Disparities Across Race/Ethnic, Income, Education and Temporal Strata in U.S. Men**
Bruce Leistikow

33. **The Cancer Care Network Clinical Trials Program: Rising from the Camp Fire Ashes**
Ofilio Vigil, Dana Little, Kristin Mensonides, Richard Bold

34. **Symptoms and Mask Use Reported in the B-Safe Pregnancy Cohort to Examine Wildfire Exposure Health Impacts**
Rebecca J Schmidt, Amanda J Goodrich, Sean Raffuse, McKenzie Oliver, Daniel Young

35. **Upper Extremity Deep Vein Thrombosis in Acute Leukemia and Non-Hodgkin's Lymphoma: Analysis of the California Cancer Registry**
Christina Poh, Ann Brunson, Theresa Keegan, Ted Wun, Anjlee Mahajan

36. **A Multi-Level Approach to Accelerating the Human Papillomavirus (HPV) Vaccine at a Rural Clinic for Native and non-Native Youth**
JHT Dang, D LeTran, A Gori, A Mojadedi, T Martens,S McClure, I Wadhwa, C Austin, MS Chen Jr.

37. **Evaluation of "Focus on HBV" through HALO's Academy for Medical Assistants**
Moon S. Chen, Jr., Mary Pat Pauly, Amy Beste-Fong, George Yang, Duke LeTran, Alexandra Gori, Kit W Tam, Ian Johnson

38. **Cancer Care Delivery in a Complex Sociotechnical Ecosystem: Communication Challenges and Opportunities**
Shin-Ping Tu

FRIDAY POSTER PRESENTATIONS (INDEX)

1. **Accelerating Therapeutics for Opportunities in Medicine**
   Brian Bennion, Izumi Hinkson, and ATOM team members

2. **Hybrid Plasmonic Biomaterial Nanofilter Scaffold for Cancer EV Diagnostics Based on Surface-Enhanced Raman Scattering (SERS)**
   Hanna J Koster, Tatu Rojalin, Juanjuan Liu, Sebastian Wachsmann Hogiu, Randy P Carney

3. **A Reliable LC-MS/MS Method for the Quantification of Natural Amino Acids: Method Validation and Application to Studies on Amino Acid Metabolism in Carcinoma Cells and during Tumor Progression**
   Zhenzhen Liu, Mei-Juan Tu, Chao Zhang, Joseph L. Jilek, Qian-Yu Zhang, Ai-Ming Yu

4. **Discovery of a Novel Fluorescent-Activating Peptide that Binds to CFA/1 Fimbriae of the Bacteria or Cancer Cells Through the Use of a One Bead One Compound (OBOC) Technology**
   Aman Singla, Shabnam Jafari, Kit S Lam

5. **Two-Tiered Platform for Sequence-Specific Identification of Nucleic Acid Biomarkers in Complex Biological Fluids**
   Mashari Alangari, Jovana Veselinovic, Yuanhui Li, Juan Manuel Artés, Zimple Matharu, Erkin Seker, Joshua Hihath

6. **Nanoporous Gold Electrode Arrays for Nucleic Acid-Based Electrochemical Biosensors**
   Jovana Veselinovic, Suzan Almashtoub, Erkin Seker

7. **Characterization of Electric Fields at Cancer Tissue and Cancer Cell Migration in Electric Fields**
   Kan Zhu, Nicholas Hum, Brian Reid, Qin Sun, Gabriela Loots, Min Zhao

8. **Epigenetic Mechanisms Underlying the Carcinogenic Effects of Circadian Clock Disruption**
   Christine A Tabuloc, Joanna C Chiu

9. **Identifying New Genes Involved in TNBC Through CRISPR Activation Screens**
   J Antonio Gomez, David J Segal, Colleen Sweeney

10. **DUET: Novel Slide-Scanning Approach for Spatially Mapping Collagen Distribution in Breast Cancer Biopsies**
    Farzad Fereidouni, Alexander Borowsky, Richard Levenson

11. **Targeted Imaging of Tumor Associated Macrophages**
    Junhan Zhou, Esther Chen, Wendy Liu, Angelique Y Louie

12. **Initial Quantitative Evaluation of Oncologic Patients Using uEXPLORER 18F-FDG PET/CT Scans**
    Yasser G Abdelhafez, Benjamin Spencer, Jeffrey Schmall, Simon Cherry, Ramsey D Badawi, Lorenzo Nardo

13. **The Potential Benefits of Using the EXPLORER Total-Body PET Scanner for Paediatric Imaging**
    Michael Woodward, Benjamin Spencer, Simon R. Cherry

14. **Exploring the Potential of uEXPLORER for Half-millisievert PET/CT Imaging**
    Guobao Wang, Jinyi Qi, Lorenzo Nardo, Macio Malogolowkin, Simon R Cherry, Ramsey D Badawi

15. **Developing a Novel Dosimetry for Liver Cancer Radioembolization Using Hepatic Artery Blood Flow Simulation**
    Amirtaha Taebi, Bahman S Roudsari, Catherine T Vu, Emilie Roncali

16. **Quantifying Drug Delivery to Single Tumor Cells in a 3D in vitro Model of the Tumor Microenvironment**
E Fong, N Hum, K Martin, BS Shergill, A Anand, V Shirure, T Ognibene, SC George

17. **Optics-Based Sensors for Magnetic Nano-Bead Detection and Cancer Tissue Imaging with Magnetic Signature as Contrasts**
Xiangdong Zhu, Yuanpei Li, Kit S Lam

18. **Nano-SN-38/Vincristine Against Pediatric Cancers**
Wenwu Xiao, Ruiwu Liu, Yuan Sun, Yanyu Huang, Noriko Satake, Kit S Lam

19. **Thermo-Responsive pNIPAM Nanoparticles as a New Strategy to Deliver the Chemotherapeutic Agent Piplartine and Anti-Inflammatory Peptide YARA in the mammary Gland for Low-Grade DCIS Treatment**
Vanessa F C Dartora, Marcus Deloney, Tanaya Walimbe, Luciana B Lopes, Alyssa Panitch

20. **Generation of Nano-therapeutic approaches for oncogenic herpesvirus mediated cancers**
Kang-Hsin Wang, Hao Wu, Yuanzhi Lyu, Christopher Chen, Michiko Shimoda, Yuanpei Li, Yoshihiro Izumiya

21. **Genomic looping formation between KSHV latent chromosomes and Host Chromosomes; Identification of Preferential Docking Sites for Latency Establishment**
Mel Campbell, Ryan R Davis, Yuichi Yanagihashi, Clifford G Tepper, Yoshihiro Izumiya

22. **Marek's Disease Virus Capture Hi-C with Chicken Lymphomas Revealed Multiple Integrated MDV Genomes with Possibilities of Vertical Infections**
Yoshihiro Izumiya, Ryan R Davis, Clifford G Tepper, Sanjay Reddy, Mel Campbell

23. **Exploiting Lysosome-Mediated Cell Death in Cancer Therapy**
Anastasia Berg, Ashley Rowson-Hodel, Kacey VanderVorst, Jenny Chen, Michelle Hu, Megan Showalter, Hao Wu, Yuanpei Li, Oliver Fiehn, Kermit Carraway

24. **Wnt/Planar Cell Polarity Signaling Promotes Breast Carcinoma Cell Collective Migration and Invasion**
Kacey VanderVorst, Jason Hatakeyama, Courtney Dreyer, Kermit Carraway III

25. **Wnt/Planar Cell Polarity Signaling Contributes to Glioblastoma Multiforme Invasiveness**
Courtney A Dreyer, Kacey VanderVorst, George Bell, James Angelastro, Sean Collins, Kermit L Carraway, III

26. **Using Advanced Mass Spectrometry Techniques to Explore Novel Metabolic Differences in Varying Grades of Meningiomas**
Zachary Rabow, Hailey Heil, Megan Showalter, Taryn Morningstar, Oliver Fiehn, Mirna Lechpammer

27. **Targeting mitochondrial metabolism for selective death of glioblastoma stem-like cells**
Sandipan Datta, Thomas Sears, Kevin Woolard, James Angelastro, Gino Cortopassi

28. **Mitochondrial Heterogeneity in Patient-Derived Glioblastoma Stem-Like Cells**
Sandipan Datta, Thomas Sears, Fiona Buchanan, Gino Cortopassi, Kevin Woolard, James Angelastro

29. **RAD51: A Promising and Novel Target for Anticancer Therapy**
Nina Nelson, Cristabelle De Souza, Harikumara Kathi , Dan Aki, Neeki Tahmassebi, Jeremy Chien

30. **The Effect of Germline Polymorphisms on Somatic Hotspot Mutations in TP53 in Cancer**
Cristabelle De Souza, Jill Madden, Devon Koestler,Dennis Minn, Jeremy Chien

31. **Effectiveness of Etravirine and Sunitinib-Based Therapy for Cell Lines Resistant to ER Stress**
Harikumara Kathi, Cristabelle De Souza, Dan Aki, Neeki Tahmassebi, Nina Nelson, Jeremy Chien

32. **Analysis of TIGAR Expression Across a Panel of Ovarian Cancer Cell Lines and Organoid Samples**
Bhavna Trehan, Cristabelle De Souza, Harikumara Kathi, Jeremy Chien

33. **Transcriptomic Characterization of 2D and 3D in vitro Models of Pancreatic Ductal Adenocarcinoma Under Hypoxia**
Ali Aliyari, Stephen J Libertini, Chang-il Hwang, John D McPherson

34. **XY018 for the Treatment of Muscle Invasive Bladder Cancer**
Christopher Lucas

35. **Tumor suppressor p14ARF depletion promotes apoptosis in prostate cancer cells**
Christopher Lucas

36. **Safety and Efficacy of a Novel Immunotherapy Strategy Incorporating Epacadostat, Intralesional SD-101, and Radiotherapy Demonstrating Activity in Checkpoint Refractory Patients**
James Liu, Christina Poh, Jingran Ji, May Cho, Xiao Zhou, Mehrdad Abedi, Joseph Tuscano, Edward J Kim, Karen Kelly, Helen Chew, Mamta Parikh, Mili Arora, Shyam Rao, Megan E Daly, Ghaneh Fananapazir, Sima Naderi, Thomas Loehfelm, Robert J Canter, Michael S Kent, William J Murphy, Arta M Monjazeb

37. **Treatment Patterns and Survival in Very Elderly Patients with Diffuse Large B-Cell Lymphoma, a Population-Based Study**
Frances B Maguire, Qian Li, Cyllene R Morris, Arti Parikh-Patel, Theresa HM Keegan

THURSDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>> BIOENGINEERED miR-328-3P MODULATES GLUT1-MEDIATED GLUCOSE UPTAKE AND METABOLISM TO EXERT SYNERGISTIC ANTIPROLIFERATIVE EFFECTS WITH CHEMOTHERAPEUTICS

Mei-Juan Tu[1], Wan-Yong Yi[1,2], Zhenzhen Liu[1], Chao Zhang[1], Ai-Xi Yu[2], Ai-Ming Yu[1]

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MicroRNAs (miRNA or miR) are small noncoding RNAs derived from genome to control target gene expresion. Recently we have developed a novel platform that offers high-yield production of bioengineered miRNA agents (BERA). This study was to produce and utilize novel fully-humanized biologic miR-328-3p molecule (hBERA/miR-328) to delineate the role of miR-328-3p in the control of nutrient uptake essential for cell metabolism. We first demonstrated successful high-level expression of hBERA/miR-328 in bacteria and purification to a high degree of homogeneity (> 98%). Biologic miR-328-3p prodrug was selectively processed to miR-328-3p to suppress the growth of highly-proliferative human osteosarcoma (OS) cells. Besides GLUT1/SLC2A1, we identified and verified LAT1/SLC7A5 as a direct target for miR-328-3p. While reduction of LAT1 protein levels by miR-328-3p did not alter the homeostasis of amino acids within OS cells, suppression of GLUT1 led to a significantly lower glucose uptake and decline in intracellular levels of glucose and glycolytic metabolite lactate. Moreover, combination treatment with hBERA/miR-328 and cisplatin or doxorubicin exerted a strong synergism in the inhibition of OS cell proliferationin. These findings support the utility of novel bioengineered RNA molecules and establish an important role of miR-328-3p in the control of nutrient transport and homeostasis behind cancer metabolism.

<<2>> A NOVEL INTEGRATED PK/PD MODEL FOR ASSESSING COMBINATION THERAPY

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Background and Aims: Current pharmacodynamics (PD) modeling of *in vivo* combination therapy offer variable results without considering actual contributions to the suppression of disease from individual drugs as well as pharmacokinetics (PK). We aim to develop a new integrated PK/PD model to assess combination drug therapy by introducing and estimating individual drug contribution factors, and establish a new formula to define combination factor. We aim to use doxorubicin (Dox) and sorafenib (Sor) antitumor therapy as an example to establish and validate this new strategy.

Methods: Dox (Drug A) and Sor (Drug B) PK data were obtained after administration of Dox (0.06 mg, i.v.) and Sor (0.02 mg, i.v. and 0.2 mg, p.o.), respectively, to BALB/c mice. Dox and Sor mono- and combination therapy data were those we published recently (Jian et al, 2017). Following the establishment of well-fitted PK models for individual drugs, PK models were integrated into the PD model for the suppression of tumor growth with three transit phases. During combination therapy, inhibition contribution from drug A and B are defined by contribution factor α and β, respectively, which were utilized along with corresponding PK (exposure, AUC) and PD (potency, k_2) properties to determine the combination factor, δ. The PK/PD model was used to simulate the efficacies of different combination regimens to achieve optimal outcomes.

Results: Both drugs' PK were fit well to two-compartment PK model. Antitumor potency of Dox was stronger than Sor during monotherapy. According to the estimated PK/PD parameters, the combination factor δ was determined as 1.24, suggesting a synergism between Dox and Sor. Simulation studies indicated that a 2-fold lower dose of Dox with 2-fold higher dose of Sor (0.5Dox+2Sor) might produce a stronger antitumor effect than current regimen (D+S).

Conclusions: A new formula considering both PK and PD properties of individual drugs as well as separate contributions was established for the assessment of combination factor, which revealed a synergism for Dox

plus Sor combination therapy in orthotopic osteosarcoma xenograft mouse models. The integrated PK/PD model is useful for identification of proper dosage regimens to achieve optimal therapeutic outcomes.

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<<3>> CAN CENTROSOME ABNORMALITIES LEAD TO CANCER?

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Centrosomes are the major microtubule-organizing center (MTOC) of the cell and are critical for bipolar spindle assembly and accurate chromosome segregation. Centrosome duplication is cell-cycle regulated and is the first step in spindle formation Defects in duplication or function lead to chromosome instability, aneuploidy, and/or polyploidy, which is common in many types of cancers. In *Saccharomyces cerevisiae* the spindle pole body (SPB) is the sole MTOC, nucleating both cytoplasmic and nuclear microtubules. Spc110 is an important homodimer protein that spans between the inner and central plaque of the SPB. Spc110 N-terminus binds and activates the gamma tubulin complex, allowing nuclear microtubule polymerization to occur. Spc110 C-terminus binds the central plaque proteins, Spc42, Spc29, and calmodulin, thus tethering the gamma tubulin complex to the SPB. Here we describe the Spc110 C-terminus domains required for SPB localization. Disruption of the Spc29, Spc42, or Calmodulin binding sites on the Spc110 C-terminus causes Spc110 to not localize to the SPB. We also examined the toxic phenotype caused by the overexpression of Spc110 C-terminus. Spc110 C-terminus overexpression (residues 741-944) causes spindle pole body defects and microtubule disruption, as it competes out endogenous Spc110 from the SPB.

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

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Homologous recombination (HR) is a template-dependent high-fidelity pathway that functions to accurately repair the DNA damage and thereby help maintain genome integrity. Loss of HR in somatic cells, leads to genomic instability and tumorigenesis whereas in germ cells, it leads to *de-novo* mutation, aneuploidy, miscarriages and infertility. Breast cancer susceptibility protein, BRCA2 plays a central role in regulating HR. BRCA2 localizes to the site of DNA damage and recruits RAD51 in somatic cells and, DMC1 as well as RAD51 in meiotic cells, to nucleate these proteins into filaments. The RAD51/DMC1 filaments function in the two signature steps of HR: 1) homology search for a DNA template and 2) DNA strand invasion. Loss of BRCA2 function is associated with increased risk of breast, ovarian and other cancers.

SYCP3 is an essential structural component of the meiosis-specific synaptonemal complex. It is typically expressed only in germline cells (*e.g.*, in testis, ovary) but not in somatic cells. However, emerging evidence indicates that SYCP3 is mis-expressed in certain cancer cells and primary tumors, and hence SYCP3 has been termed a cancer/testis antigen. Recently, it was reported that in somatic cells SYCP3 interacts with BRCA2 and impairs recruitment of RAD51. The structural role of SYCP3 in meiosis is relatively well understood, but its potential direct role in HR and effects in somatic cells remain unclear. Our research addresses the gap in knowledge of how SYCP3 regulates BRCA2 function in germline and somatic cells.

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

Next, we establish the biochemical mechanism by which SYCP3 leads to functional loss of BRCA2/ HR in somatic cells by *in vitro* assays using purified proteins. Our results indicate direct interaction between SYCP3 and BRCA2 which impairs the BRCA2-RAD51 interaction. SYCP3 has also been shown to interact with RAD51 but the significance of this interaction is not clear. Our preliminary findings indicate that in the presence of another essential recombination protein RAD54, SYCP3-RAD51 interaction might not have any physiological effect in disrupting HR.

To understand the physiological significance of BRCA2-SYCP3 interaction during meiosis, we tagged the native *Brca2* gene with a *3xHA* affinity tag. Mice that are homozygous for *Brca2-3HA* are viable and fully fertile demonstrating that the tagged allele is fully functional. This unique reagent was employed to analyze the localization of BRCA2 during meiosis, revealing a punctate pattern along chromosome axis that was always in close association with SYCP3. The BRCA2 localization pattern is quite distinct from those of other recombination proteins such as RAD51 and DMC1. Intriguingly, BRCA2 localization was diminished in *Sycp3* mutant mice consistent with physical interaction between BRCA2 and SYCP2, and pointing to a role for SYCP3 in recruiting BRCA2 to chromosome axes. The dynamics of the RAD51 and DMC1 recombination factors is also altered in *Sycp3* mutants implying that BRCA2-SYCP3 interaction is functionally significant.

The results of our ongoing studies will establish how SYCP3 expression in somatic cells interferes with BRCA2-dependent HR.

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<<5>> EPIGENETIC REGULATION OF KSHV REACTIVATION

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Kaposi's sarcoma-associated herpesvirus (KSHV) life cycle consists of two phases, a latent and lytic cycle. Histone modifications have profound effects on KSHV gene expression thereof KSHV reactivation from latently infected cells. Recent advancements in mass spectrometry revealed a number of novel histone lysine-modifying acyl groups including propionyl, butyryl, 2-hydroxyisobutyryl, ßhydroxybutyryl, malonyl, succinyl, glutaryl, and crotonyl in tissue samples. Identification of these new competing histone lysine modification raises numerous questions on their biological significance and molecular functions. Current studies utilizing cell culture are maintained under high glucose conditions, which artificially saturate the cells with a high acetyl-CoA concentration, thereby diminishing the possible impact of other histone modifications. Recent studies indeed showed that histone crotonylation induces transcription activation more than the well-characterized histone acetylation and can reactivate HIV from latently infected cells. In this study, we examined the effects of multiple histone acylations. Among them, we found that treatment of KSHV infected cells with sodium-crotonate is sufficient to induce KSHV lytic reactivation. In addition, sodium-crotonate synergistically activates KSHV gene expression with KSHV transactivator, K-Rta. Our studies suggest that the concentration of the multiple CoA counterparts regulate histone modifications of viral chromatin at the K-Rta promoter, which sensitizes KSHV to reactivation. We propose that many metabolic processes influence the concentration of available acyl-CoA that may dictate the rate of KSHV replication via chromatin remodeling.

<<6>> MECHANISMS FOR KSHV LATENT INFECTION IN ORAL EPITHELIA WITH AN ORGANOTYPIC 3D CULTURE MODEL

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The oral cavity is the site for replication of a variety of herpesviruses, including Kaposi's sarcoma- associated herpesvirus (KSHV), and plays an important role for their propagation and spread. Previous studies have suggested that oral epithelial cells support latent infection and lytic replication of KSHV. Oral epithelium consists of a mixture of cells at different stages of differentiation. Identification of the detailed mechanisms of how KSHV establishes latent infection in oral epithelia, and which stage(s) of cellular differentiation supports lytic replication, will lead to improved understanding of the nature of the KSHV life cycle. To this end, we established an organotypic 3D culture model using primary human gingival epithelial (HGEP) cells. This culture model has a stratified structure consisting of a proliferating basal and terminally differentiated suprabasal layers, and possesses typical epithelial properties such as a high transepithelial electrical resistance. We infected the organotypic culture with recombinant KSHV and found that KSHV specifically infected the cells within the stratified epithelium; however, KSHV reactivation was seen only in the upper layers without any additional stimuli. We are currently isolating single cells from KSHV-infected organotypic cultures to perform single cell RNA-sequencing and identifying key cellular events that trigger KSHV replication.

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<<7>> NANOMECHANICAL-PLASMONIC BIOSENSOR FOR THE DETECTION OF TUMOR-SPECIFIC EXOSOMES

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The proposed platform is a novel infrared (IR) spectroscopy-based nanomechanical transducer-on-a-chip with unprecedented sensitivity tailored specifically for the detection and profiling of tumor-derived exosomes (TEXs) from human ovarian cancer (OvCa) patients. The fundamental detecting block combines a thin freestanding piezoelectric slab of aluminum nitrate (AlN, ~400 nm) with a nanopatterned gold (Au) metasurface that together forms a new transduction mechanism merging tailored optical and electromechanical resonances with the high sensitivity of surface plasmons. The operation principle of the sensor is illustrated in Fig. 1. This technology was recently demonstrated by one of the PIs (Nat. Com. 7, 11249, 2015) to detect infrared light over a narrowband, significantly outperforming alternatives approaches as Fourier Transform IR (FTIR) systems at room temperature. Yet, until now, the platform has not been applied to bio-sensing, therefore is considered high-risk but with potential for significant improvement over currently available methods (such as FTIR and sandwich-ELISA) in terms of sensitivity, speed, cost, and portability. The miniaturized size of each detector (~150 μm x 50 μm x 500 nm per device) will be exploited in array configurations to ***simultaneously test multiple TEXs fingerprints on a single silicon chip***.

Fabrication and characterization of a wafer containing over 350 detectors was recently carried out at the UC Davis Center for Nano-MicroManufacturing (see Fig. 2). Aiming to demonstrate the reproducibility of the device, we tested 150 devices with identical geometrical features obtaining a nanomechanical factor of 2’112 with a standard deviation of ±57. This mechanical response is remarkable and in agreement with the latest reports from the NMEMS state of the art. The gold surface of the detector was patterned at the nanoscale to absorb very specific wavelengths within the infrared. Fig. 2c shows the optical image of a given detector and an SEM image of the nanopatterning realized on top. Our numerical simulations and preliminary experimental

characterization show that the device can easily be tailored to exhibit a maximum absorption at desired wavelengths. We are currently testing the performance of the fabricated sensor. Specifically, we are analyzing their response for the label-free detection of exosomes. To this purpose, we fabricated several sensors tailored to the vibrational modes (spectral fingerprints) of exosomes. In addition, to enhance the platform sensitivity, we fabricated sensors able to easily detect infrared flares (IRFs) that behave as absorbing nanoprobes bound to vesicles. We expect to report experimental data in the near future.

This CTP Award has allowed the PIs to put forward a UC Cancer Research Coordinating Committee project that has recently been funded. Two additional projects submitted to NIH (R21) were not funded.

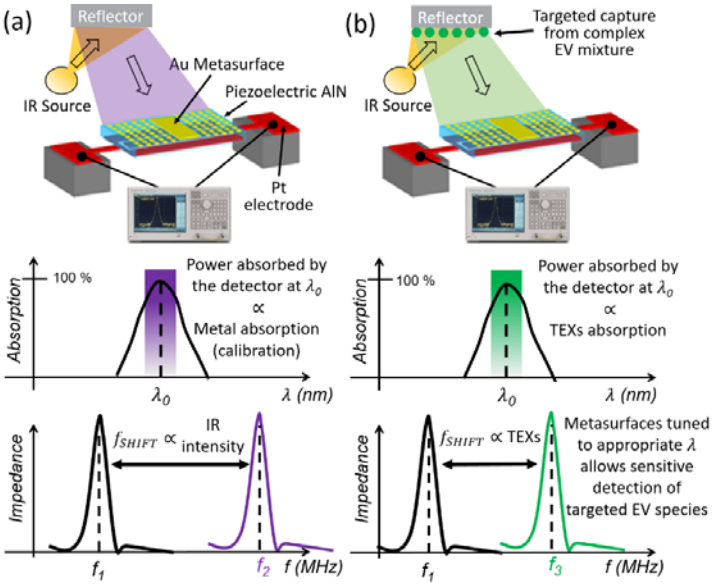

Figure 1: Operation principle and novel transduction mechanism of the developed biosensor. (a) The mechanical resonance frequency of the free-standing piezoelectric slab is measured at MHz in the absence of analytes (f_1). A specific wavelength (λ_0) of an impinging IR beam is bounced from a gold reflector and absorbed by the device, heating it up and leading to a shift in intrinsic mechanical resonance frequency (f_2). (b) The refractive index of the EVs captured by the functionalized reflector modifies the reflected IR beam and the power absorbed by the sensor, tuning the shift in the resonance frequency. This shift permits accurate, sensitive identification of the absorbed analytes.

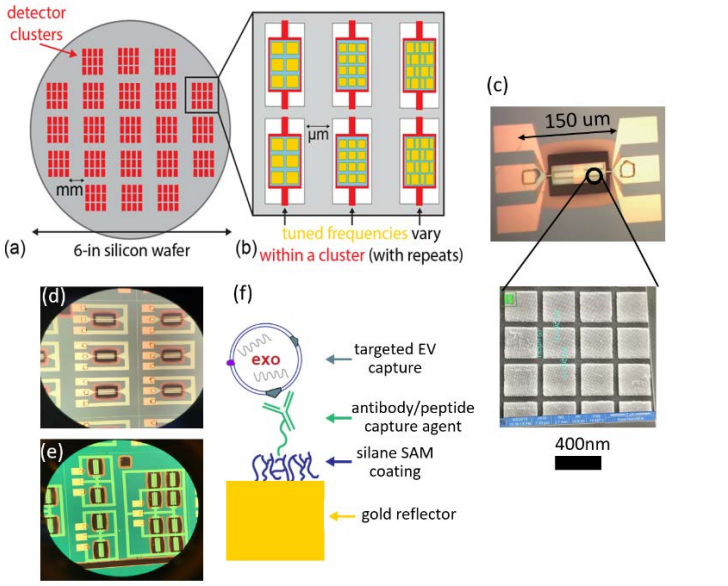

Figure 2: Scheme for detector layout and functionalized reflector. (a) A single wafer feature dozens of detector clusters spaced a few mm. (b) Within a single cluster, dozens of individual free-standing detectors can be tuned to various EV- or IRF-specific frequencies, with several repeats for a given frequency to build up statistics. (c) Optical image of a detector before being tested in a probe station (top) and SEM image of the metasurface placed on top (bottom). (d)-(e) Optical images showing fabricated individual detectors and clusters of them. (f) Gold reflector chemically modified with EV capture agents, potentially with a silane SAM coating to reduce non-specific absorption and improve surface coverage.

<<8>> A POLH TRANSCRIPT WITH A SHORT 3'UTR ENHANCES PoLH EXPRESSION AND MEDIATES CISPLATIN RESISTANCE

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Platinum-based anticancer drugs are widely used as a front line drug for cancers, such as non-small-cell lung carcinoma (NSCLC) and bladder cancer. However, the efficacy is limited due to intrinsic or acquired resistance to these drugs. DNA polymerase eta (PolH, Polη) belongs to the Y-family of DNA polymerases and mediates DNA translesion synthesis, a major mechanism for DNA damage tolerance. Here, we showed that a high level of PolH is associated with cisplatin resistance in lung and bladder cancer. Consistent with this, loss of PolH markedly attenuates cisplatin resistance in both cisplatin-sensitive and -resistant lung cancer cells. Interestingly, we found that due to the presence of multiple polyadenylation sites, alternative polyadenylation (APA) produces three major PolH transcripts with various lengths of 3'untranslated region (3'UTR) (427-/2516-/6245-nt). We showed that the short PolH transcript with 427-nt 3'UTR is responsible for high expression of PolH in various cisplatin-resistant lung and bladder cancer cell lines. Importantly, loss of the short PolH

transcript significantly sensitizes cancer cells to cisplatin treatment. Moreover, we found that miR619 selectively inhibits the ability of the long PolH transcript with 6245-nt 3'UTR to produce PolH protein and subsequently, PolH-dependent cell growth. Together, our data suggest that PolH expression is controlled by APA and that the short PolH transcript produced by APA can escape miR619-mediated repression and subsequently, confers PolH-mediated cisplatin resistance.

<<9>> AN ERBB4 5'UTR HAPLOTYPE IS ASSOCIATED WITH REDUCED LIFESPAN IN GOLDEN RETRIEVERS

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Cancer is the leading cause of death in Golden Retrievers. Recent estimates of cancer associated mortality in the breed is in excess of sixty-percent, with reported median lifespans ranging from 9-12 years of age. Genome wide association (GWAS) data comparing golden retriever (GR) dogs that died of cancer before the age of 12 and GRs that lived longer than 14 years identified a highly associate SNP within the canine ERBB4 gene (OR 7.737). Whole genome sequencing data on a subset of those dogs identified 3 distinct haplotypes characterized by indels located upstream of the canine ERBB4 annotated transcription start site. Varying copies of a 6-base-pair repeat differentiated the three haplotypes, and haplotype 3 had two additional deletions spanning 6 and 18-base-pairs that flanked the 6-base pair repeat. Additional DNA fragment analyses of 231 GR DNA samples, including those in the original GWAS, found that dogs carrying two copies of haplotype 1 were more likely to live to age 12 compared to GRs with 2 copies of haplotype 3 ($p < 0.01$, 95% CI 0.21-0.81), suggesting the unique deletions in haplotype 3 may be a contributing factor. Transcription factor binding analyses revealed that one of the deletions, the 6-base pair deletion, represented a core motif of the dioxin response element (DRE), which is the binding site for the transcription factor aryl hydrocarbon receptor (AHR). Preliminary data shows that canine ERBB4 is down regulated in canine cell lines treated with the AHR agonist indol-3-carbinol (I3C), suggesting AHR regulation of ERBB4 and a potential functional role for the 6-base pair deletion in haplotype 3 that was associated with cancer mortality. Additional studies are underway to further examine the role of the haplotype sequence indels.

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<<10>> HIGH-QUALITY POSITRON EMISSION TOMOGRAPHY (PET) FOR EARLY TREATMENT RESPONSE ASSESSMENT IN RADIOTHERAPY

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The goal of this ongoing exploratory project is to generate preliminary data on changes in quantitative ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging measurements early during a course of radiotherapy (RT) using a canine model and the world's first total-body PET scanner (mini EXPLORER II). Our working hypothesis is that changes in quantitative PET metrics early during RT are associated with clinical outcomes.

^{18}F-FDG PET imaging after treatment has been widely accepted for late response assessment in several types of cancer, which serves as a late predictor of clinical outcomes to guide patient care after treatment. ^{18}F-FDG PET imaging during a course of treatment may serve as an early predictor of treatment response and outcomes, and thereby potentially allow response-adapted therapy (*e.g.*, biologically adaptive RT). However, there have been only several small studies on the prognostic value of ^{18}F-FDG PET during treatment. These studies report conflicting results, which can be explained in part by substantial uncertainties in conventional PET imaging, arising from many factors including physical factors that depend largely on performance of the PET system (*e.g.*, limited spatial resolution and signal-to-noise ratio). The EXPLORER system has a 24-fold gain in effective sensitivity over conventional scanners, and thereby allows image reconstruction at substantially higher spatial resolution and signal-to-noise ratio. Thus, quantitative ^{18}F-FDG PET metrics

measured by the EXPLORER system may provide improved prognostic value compared to conventional scanners.

In the ongoing canine clinical trial, we will quantify: (1) test-retest repeatability of quantitative PET metrics based on repeat scans acquired before RT; and (2) changes in quantitative metrics based on repeat scans acquired early during RT (after 6-9 Gy and 15-18 Gy) for canines with spontaneously arising head and neck tumors receiving RT (≥51 Gy in 3 Gy daily fractions). Imaging involves a low-dose CT scan for PET attenuation correction, followed by a 60-min dynamic PET scan starting simultaneously with ^{18}F-FDG injection. We will calculate global standardized uptake value (SUV)-based metrics (*e.g.*, SUV_{max}) as well as kinetic parameters (^{18}F-FDG delivery and trapping) at each time point, and then quantify changes in those metrics. Moreover, we will perform parametric response mapping to calculate a percentage of tumor volume that show increased, unchanged, or decreased SUV values. We plan to present data of the first subject at the symposium.

Acknowledgments: This study is supported in part by the Center for Companion Animal Health, UC Davis School of Veterinary Medicine and UC Davis Comprehensive Cancer Center.

<<11>> DEVELOPMENT OF A THERANOSTIC FOR PET IMAGING AND RADIOTHERAPY OF BRAIN CANCER

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Overexpression of α3β1 integrin has been reported in several cancer types including glioblastoma, and has been associated with poor prognosis, tumorigenesis, tumor invasion, increased metastatic potential, and resistance to treatment. Thus, α3β1 integrin is both a promising cancer-specific biomarker and a possible therapeutic target. LXY30, a cyclic peptide with the sequence cdG-Phe(3,5-diF)-G-Hyp-NcR, binds to several α3β1 integrin-expressing glioblastoma cancer cell lines with high affinities (low nM) and demonstrates *in vivo* tumor-targeting effects in glioblastoma xenograft mouse models using optical imaging. In order to further investigate the potential of LXY30 as a human tumor-targeting peptide ligand for systemic and intracranial delivery of imaging agents and cancer therapeutics, here we report the development of LXY30 into a new theranostic for brain cancer. We envision that this novel LXY30 theranostic conjugate will have high clinical impact in, not only brain cancer, but also many other tumor overexpressing α3β1 integrin. In this CCSG-supported pilot project, we have developed a convenient and practical method for dual radiolabeling of LXY30, either with radiometal such as ^{64}Cu or [^{18}F]Fluoro-benzoic acid-NHS. In order to minimize non-specific binding, improve water solubility and increase circulating half-life in vivo, we added a hydrophilic stealth peptide linker (-ekekekekek-) between LXY30 and the radiolabel (^{64}Cu or ^{18}F). NOTA was chosen as a metal chelator for ^{64}Cu loading and PET imaging due to its high in vivo stability than DOTA and less harsh condition for radiolabeling than CB-TE2A. In addition, NOTA has been successfully used as a ^{64}Cu chelator to radiolabel AE105 for PET imaging of urokinase-type plasminogen activator receptor (uPAR) expression in glioblastoma and phase 1 clinical trial showed promising results. The LXY30-FBA-NOTA conjugate with the stealth linker was successfully synthesized using a standard solid phase peptide synthesis approach. Radiolabeling the conjugate with ^{64}Cu was successfully achieved and preliminary PET images were obtained in GL261 glioblastoma mice. The results will be presented.

Acknowledgments: This work was funded by the UC Davis Comprehensive Cancer Center CCSG IRG Pilot Funding.

<<12>> ISOCITRATE DEHYDROGENASE MUTANT GLIOBLASTOMA IS PREFERENTIALLY RELIANT ON HDAC ENZYME ACTIVITY FOR MAINTENANCE OF CELLULAR PROLIFERATION AND SURVIVAL

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Glioblastoma (GBM) is an incurable form of brain cancer with a median survival of ~15 months after treatment with chemoradiotherapy. Identification of a CpG Island Methylator Phenotype (CIMP) subtype of GBM (G-CIMP), represents a significant clinical discovery, as these patients have an enhanced survival, with a median survival of 3 years. G-CIMP is characterized by a mutation in isocitrate dehydrogenase 1 or 2 (IDH1/2) which results in production of the oncometabolite 2-hydroxglutarate, an inhibitor of α-ketoglutarate-dependent demethylases. This mutation occurs early in gliomagenesis and further results in aberrant DNA methylation and transcriptional repression. Knowing that histone deacetylase (HDAC) enzymes are localized to methylated chromatin via methyl-binding domain (MBD) proteins, we hypothesized that IDH mutant GBM may be preferentially dependent on HDAC enzyme function for cellular proliferation and survival. Indeed, we show that G-CIMP is significantly more sensitive *in vitro* to the clinically approved pan histone deacetylase (HDAC) inhibitor panobinostat, with IDH mutant GBM cells exhibiting ~4 and ~9 fold lower EC50 values in flow cytometric cell viability and apoptosis assays compared to IDH wild type GBM cells, respectively. For IDH mutant GBM, the average EC50 values were 13.5 nM for cell viability and 4.8 nM for apoptosis assays. This sensitivity was not observed in cell viability and apoptosis assays utilizing the ribosomal inhibitor puromycin, refuting the alternative hypothesis that IDH mutant GBM cells are more generally sensitive to cell death mediated by cellular stressors. Induction of cleaved caspase 3, a marker of apoptosis, was observed only in IDH mutant GBM cells when exposed to 10 nM panobinostat over 5 days. Analysis of proliferation via Brdu incorporation assays show that proliferation of IDH mutant GBM was reduced by over 80% with exposure to 10 nM panobinostat for 48 hours, whereas the same dose and exposure in wild type IDH GBM only reduced cellular proliferation by ~25%. Analysis of cell cycle alterations upon exposure to 20 nM panobinostat for 48 hours showed that G1 arrest was induced only in IDH mutant cell lines, but not IDH wild type GBM. Further western blot analysis shows that various acetylated chromatin marks, i.e. H3K9/14/18/27Ac, are preferentially upregulated in our IDH mutant GBM cell lines when exposed to 10 nM panobinostat for 48 hours. This supports the hypothesis that IDH mutant GBMs are more sensitive to panobinostat via higher basal HDAC activity, though this is not conclusive until further evaluation. These data ultimately suggest that G-CIMP tumor cells are reliant on established epigenetic programs for cellular proliferation and survival, and that HDAC enzymes may play a critical role in maintaining this epigenetic state. These studies provide a strong foundation for future preclinical work evaluating the prospective treatment of G-CIMP with HDAC inhibitors.

<<13>> COMPUTATIONAL MODELING AND MATERIAL DESIGN OF AN INTRACRANIAL TUMOR TREATMENT FIELD SYSTEM IN A RODENT

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Introduction: Glioblastoma multiforme (GBM) is a highly malignant brain tumor with a median survival of 15 months. Tumor treating fields (TTFields) are a novel treatment modality for GBM consisting of low intensity (1-2V/cm), alternating electrical fields that disrupt mitosis in cancer cells. The current extracranial system has several limitations including: large energy requirements (60V), field heterogeneity near the tumor, discontinuous therapy, and psychosocial burdens due to the device appearance and shaving of hair. We propose a new modality for generating TTFields using a miniaturized implanted intracranial system inside the brain to address the limitations of the extracranial device. Towards this goal, we present a computational modeling and material design study of intracranial electrodes coated with different insulators to analyze the electric field intensities achieved and the expected energy requirements.

Methods: COMSOL Multiphysics software was used to develop a spherical tumor inside the grey matter of a rat brain flanked by 0.2mm diameter tungsten electrodes insulated by an insulator. The electrodes are designed using a 10mm long wire that is folded in half, allowing for a completely insulated electrode tip and to increase surface area. Permittivity constants for glioma tumor, grey matter, tungsten electrodes,

polyimide(dielectric=3), and BaTio3(dielectric=10000) were applied to each object. The electrostatic model was solved for the field intensity generated between a 3 by 3 electrode array configuration with the following parameters: alternating current, 50V potential difference, frequency 200 kHz.

Results: The polyimide insulated electrodes achieved 1V/cm field intensity within 0.05mm of the electrode array and did not achieve therapeutic fields within the tumor or the peritumoral tissue. The BaTio3 insulated electrodes achieved 5-7V/cm in 100% of the tumor and the peritumoral tissue.

Conclusion: Our computational model predicts that high dielectric insulating materials such as BaTio3 are superior to conventional insulating materials in achieving therapeutic TTFields using intracranial electrodes. These results suggest that an implanted rodent TTFields system is feasible, effective, and energy efficient.

<<14>> UPREGULATION OF CYSTEINE METABOLITES IN IDH-1 MUTANT AND MGMT METHYLATED HIGH-GRADE GLIOMAS

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Background and Aims: Isocitrate dehydrogenase (IDH) mutation imposes in gliomas a shortage of NADPH required to maintain a redox state, so these tumors may show increased dependence on the transsulfuration (TS) pathway (CBS, CSE) to produce signaling molecules (H_2S, taurine) needed to ensure antioxidant levels critical for their survival and growth.

The first aim of this study was to determine cystathionine B-synthase (CBS, the brain's main H_2S producing enzyme) expression in astrocytomas and its correlation with histopathological grade.
The second aim was to investigate alterations of cysteine (Cys) metabolites in genetic variants of high-grade gliomas (HGG).

Patients and Methods: In the 1st cohort, newly diagnosed astrocytomas from 22 adult patients were retrospectively reviewed for CBS expression by immunohistochemistry (IHC) and staining scores were determined (H-score; range: 0 – 300). In the 2nd cohort, 17 HGG samples from 15 adult patients were analyzed by HPLC, and levels of Cys, homocysteine and glutathione (GSH) were correlated with the genetic signature of HGG (wild-types vs. IDH1 mutation, PTEN deletion, EGFR amplification and MGMT methylation).

Results: In the 1st cohort, CBS was expressed in 40% (2/5) of diffuse astrocytomas (grade II); 83% (5/6) of anaplastic astrocytomas (grade III) and in 100% (11/11) of glioblastomas (grade IV), with a higher staining intensity in psudopalisading tumor cells adjacent to necrosis. Mean H-score differed in CBS expressing tumors according to their grade, yielding the lowest score of 40 in grade II diffuse astrocytomas, compared to scores of 182 and 189 in anaplastic astrocytomas and glioblastomas (grades III and IV, retrospectively).

In the 2nd cohort, Cys levels were significantly higher (2.1 fold increase; p=0.0038) in IDH1-mut (n=4) vs. IDH1-wt HGG (n=13), with comparable homocysteine and GSH levels. PTEN deletion and EGFR amplification did not significantly alter Cys metabolites. Significantly higher Cys levels (3.2 fold increase; p=0.0186) were also found in MGMT methylated (n=4) vs. non-methylated (n=3) HGG, with comparable levels of homocysteine and GSH.

Conclusions: Our results show more intense CBS expression and presumptively higher H_2S activity in astrocytomas with aggressive phenotypes (grades III and IV). These findings are consistent with detected increased Cys levels in IDH1-mut and MGMT methylated HGG supporting the hypothesis that these tumors may preferentially use the TS pathway for GSH synthesis. Nonetheless, concurrent increased intake of Cys cannot be excluded. Our results suggest utilizing Cys metabolites as potential markers and/or therapeutic targets in some genetic variants of HGG, a hypothesis that should be further explored in larger translational trials.

<<15>> DEVELOPMENT OF CD40L ANTAGONISTS THAT SUPPRESSED PROLIFERATION OF B-CELL LYMPHOMA

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CD40 ligand (CD40L) plays a major role in immune response and is a major therapeutic target for inflammation. Integrin α5β1 and CD40 simultaneously bind to CD40L. It is unclear if α5β1 and CD40 work together in CD40/CD40L signaling or how α5β1 binds to CD40L. Here we describe that integrin-binding site of human CD40L is predicted to be located in the trimeric interface by docking simulation. Mutations in the predicted integrin-binding site markedly reduced the binding of α5β1 to CD40L. Several CD40L mutants defective in integrin binding were defective in NF-kB activation and B cell activation and suppressed CD40L signaling induced by WT CD40L, while they still bound to CD40. These findings suggest that integrin α5β1 binding to monomeric CD40L through the binding site in the trimeric interface of CD40L, and this plays a critical role in CD40/CD40L signaling. Integrin αvβ3, widely distributed vascular integrin, bound to CD40L in a KGD-independent manner, suggesting that αvβ3 is a new CD40L receptor. Several missense mutations in CD40L that induce immunodeficiency with higher-IgM syndrome type 1 (HIGM1) are clustered in the integrin-binding site of the trimeric interface. These HIGM1 CD40L mutants were defective in binding to α5β1 and αvβ3 (but not to CD40), suggesting that the defect in integrin binding may be a causal factor of HIGM1. These finding suggest that α5β1 and αvβ3 bind to the overlapping binding site in the trimeric interface of monomeric CD40L and generate integrin-CD40L-CD40 ternary complex. CD40L mutants defective in integrins have potential as antagonists of CD40/CD40L signaling (CD40L decoys) in chronic inflammatory diseases and cancer. We showed that CD40L decoys (e.g., Y170E mutant) suppressed proliferation of B-cell lymphoma Ramos induced by wild-type CD40L. Therefore, CD40L decoys cam be used as therapeutics in cancer. We are going to test the potential of stabilized CD40L decoy (CD40L decoy fused to Fc, expected half-life 14 days) for cancer treatment in future experiments.

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Takada, Y.K., J. Yu, M. Shimoda, and Y. Takada, *Integrin Binding to the Trimeric Interface of CD40L Plays a Critical Role in CD40/CD40L Signaling.* J Immunol, 2019. 10.4049/jimmunol.1801630

<<16>> GENERATING A CELL BASED ASSAY FOR HIGH CONTENT SCREENING OF SMALL MOLECULES AND PROTAC MOLECULES

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Introduction: Galectin-1, a β-galactoside binding protein from the galectin family, is significantly overexpressed in different types of cancers, such as pancreatic ductal adenocarcinoma, kidney cancer, ovarian cancer, lung cancer, breast cancer, etc. High expression of Galectin-1 and Galectin-3 leads to angiogenesis of tumors, apoptosis of T-cells, cell proliferation of tumors through the RAS pathway, and metastasis of cancer. Galectin-3, also known as gal 3, is a protein of the lectin family that binds galactose containing glycoproteins. This gene plays an important role in cancer metastasis as well through immunosuppressive mechanisms in the tumor microenvironment. Since elevated galectins actively fuel cancer, it is imperative to identify novel molecules that can target galectins for better cancer therapy. The intracellular levels of many proteins are regulated by ubiquitin-dependent proteolysis. One of the best-characterized enzymes that catalyzes the attachment of ubiquitin to proteins is a ubiquitin ligase complex. Our aim is to target galectins for ubiquitination and degradation utilizing a chimeric compound called protein-targeting chimeric molecule (PROTAC). In order to do so, we developed cell lines over-expressing galectin-1 and will conduct screening of several PROTAC molecules using the One Bead One Compound (OBOC) approach (Lam *et al*).

Experimental Procedures: In order to generate our cell-based assay, we used two plasmid constructs from *Addgene*, mCherry-Galectin, and dsRed-Galectin and exogenously introduced galectins into an immortalized cell line like HEK-293T and a cervical cancer cell line HeLa. Our construct for the galectin inhibitor screen includes mCherry and dsRed which are fluorescent proteins which also includes the neomycin (G418) resistance gene. mCherry, a fluorescent protein, is a marker to follow flow of molecules and cell components, often used in transfections. Neomycin (G418), an antibiotic, is used to treat the cells as a selection agent. Neomycin resistant cells are linked to Galectin-1 genes, which will then be treated with galectin inhibitors. Upon several rounds of G418 selection, we have identified an enriched population of cells, both in HEK and HeLa that express galectin-1 and can be used for assays. Using immunoblotting and immunofluorescence we have validated the expression of galectin-1 and mCherry in our desired cell lines thus indicating that mCherry is a good reporter system for galectin expression systems. We also analyzed the effect of galectin -1 inhibition using known galectin inhibitor, LLS30 (Shih, Liu, Lam *et al*), and thus describe an effective system for studying galectin inhibitor and degrader molecules.

Summary of Data: Our results indicate that stable expression of mCherry in both cell lines is associated with galectin-1 expression and the cell lines we generated are suitable models to screen for novel therapeutics that target galectin.

Significance: This genetic screen will enable the identification of novel molecules like PROTACs that will result in future studies on preventative and therapeutic mechanisms using galectin inhibitors as a target for enhanced cancer therapy.

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mCherry-Galectin-C-18 was a gift from Michael Davidson (Addgene plasmid # 62745 ; http://n2t.net/addgene:62745 ; RRID:Addgene_62745)
Project was conceptualized in collaboration with the Lam Lab, Department of Biochemistry and Molecular Medicine, UC Davis Medical Center.

<<17>> DEVELOPMENT OF BIOLUMINESCENT PROBES FOR VISUALIZING METAL DYNAMICS IN CANCER BIOLOGY

Justin O'Sullivan, Joseph AbouAyash, Adam Hillaire, Marie Heffern

Redox-active metals have long been recognized as essential micronutrients and their dysregulation has been associated with various disease pathologies including cancer. For example, recent studies suggest altered copper levels observed in tumor environments likely play a significant role in cancer progression on account of its involvement in cell proliferation, oxidative control, and respiration. As such, the ability to visualize the dynamic movement of these metal pools would provide key insight into mechanisms underlying cancer progression. However, current techniques for longitudinal monitoring of redox-active metals *in vivo* are lacking and limited in their selectivity, sensitivity, and spatial control. Bioluminescent imaging systems use a substrate/enzyme pair generally known as a luciferin/luciferase pair to selectively generate photons in the presence of an analyte. This is typically done by chemically modifying the luciferin, termed "caging" so that it is unable to interact with it's luciferase pair and generate light unless it is in the presence of analyte. Bioluminescent probes provide numerous advantages including high sensitivity and targeted localization. We are developing a bioluminescent imaging probe for monitoring extracellular copper pools. This presentation describes our efforts towards the chemical synthesis of the luciferin cores and the metal-responsive cages as well as assessing the effects of metals on luciferase enzyme activity.

<<18>> DOMINANCE OF METABOLIC CONTROL DETERMINES CANCER SUBTYPE-SPECIFIC RESPONSE TO THERAPEUTICS OF LIPID METABOLISM

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Tumor subtype-specific metabolic reprogrammers could serve as targets of therapeutic intervention. Here we show that triple-negative breast cancer (TNBC) exhibits a hyper-activated cholesterol-biosynthesis program that is strongly linked to nuclear receptor RORγ, compared to estrogen receptor-positive breast cancer. Genetic and pharmacological inhibition of RORγ reduces tumor cholesterol content and synthesis rate while preserving host cholesterol homeostasis. We demonstrate that RORγ functions as an essential activator of the entire cholesterol-biosynthesis program, dominating SREBP2 via its binding to cholesterol-biosynthesis genes and its facilitation of the recruitment of SREBP2. RORγ inhibition disrupts its association with SREBP2 and reduces chromatin acetylation at cholesterol-biosynthesis gene loci. RORγ antagonists cause tumor regression in patient-derived xenografts (PDX) and immune-intact models. Their combination with cholesterol-lowering statins elicits superior anti-tumor synergy selectively in TNBC. Together, our study uncovers a master regulator of cholesterol-biosynthesis program and an attractive target for TNBC.

<<19>> THERAPEUTIC TARGETING MDR1 EXPRESSION BY RORΓ ANTAGONISTS RESENSITIZES CROSS-RESISTANT CRPC TO TAXANE VIA COORDINATED INDUCTION OF CELL DEATH PROGRAMS

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Overexpression of ATP-binding cassette subfamily B member 1 (ABCB1)-encoded multidrug resistance protein 1 (MDR1) constitutes a major mechanism of cancer drug resistance including docetaxel (DTX) and cabazitaxel (CTX) resistance in castration-resistant prostate cancer (CRPC). However, no therapeutics that targets MDR1 is available at clinic for taxane sensitization. We report here that RORγ, a nuclear receptor family member, unexpectedly mediates MDR1/ABCB1 overexpression. RORγ plays an important role in controlling the functions of subsets of immune cells and has been an attractive target for autoimmune diseases. We found that its small-molecule antagonists are efficacious in re-sensitizing DTX and CTX cross-resistant CRPC cells and tumors to taxanes in both androgen receptor (AR)-positive and -negative models. Our mechanistic analyses revealed that combined treatment with RORγ antagonists and taxane elicited a robust synergy in killing the resistant cells, which involves a coordinated alteration of p53, Myc and E2F-controlled programs critical for both intrinsic and extrinsic apoptosis, survival and cell growth. Our results suggest that targeting RORγ with small-molecule inhibitors is a novel strategy for chemotherapy resensitization in tumors with MDR1 overexpression.

<<20>> ORALLY EFFECTIVE ANTAGONISTS OF NUCLEAR RECEPTOR ROR-γ INHIBIT CRPC TUMOR GROWTH AND AGGRESSIVE PROGRAMS

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Background: Patients with locally advanced prostate cancer (PCa) undergoing androgen-deprivation therapy have high chances to progress to metastatic castration-resistant prostate cancer (mCRPC). We previously discovered that retinoic acid receptor-related orphan receptor γ (ROR-γ) drives the overexpression of androgen receptor (AR) in CRPC and that ROR-γ antagonists potently block tumor growth and metastasis. Here we aimed to investigate

whether ROR-γ small-molecule antagonists are orally bioavailable and effective in inhibition of patient-derived xenograft (PDX) tumors and to identify the potential therapeutic mechanism of the ROR-γ inhibitors in CRPC.

Methods: Mice with LuCaP-35CR PDX tumors were orally administrated with different doses of small-molecule antagonists of ROR-γ or vehicle for 40 days. Tumor volume and body weight was monitored. Tumors were subjected to Immunohistochemistry (IHC) staining of Ki-67 and cleaved caspase-3. Additionally, organoids developed from PDX tumors were also treated with the antagonists for examination of cell viability. To further explore the mechanism of action (MOA) of the antagonists, RNA-seq gene expression profiling and gene set enrichment analyses (GSEA) was performed.

Result: The three ROR-γ antagonists exhibited strong potency in inhibition of LuCaP-35CR tumor growth. The antagonists also significantly inhibited the proliferation and survival of tumor organoid cells. Mechanistically, they strongly suppressed the aggressive progression pathways or programs such as those of AR-variants (AR-V) and NEPC as well as the PCa-subtyping PCS1 signature genes.

Conclusions: Our study using PDX and organoid models demonstrates the oral bioavailability and anti-CRPC potency of small-molecule antagonists of ROR-γ. ROR-γ may promote tumor cell proliferation and survival by stimulating gene programs such as the ones that are indicative of aggressive PCa subtypes (PCS1 and NEPC).

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<<21>> CHARACTERIZATION OF A NOVEL ANDROGEN RECEPTOR VARIANT, VBL-1, IN BLADDER CANCER

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Background: Bladder cancer is the sixth most common cancer in men and the seventeenth most common cancer in women. A potential mediator for this gender disparity is the androgen receptor (AR), a ligand-dependent transcriptional factor dependent on androgen binding. Cell and tumor cancer models, however, have an increase in AR splice variants, some of which lack a ligand binding domain, but retain their ability to bind DNA and activate transcription. We have isolated and characterized a mutated AR variant, VBl-1, in human bladder cancer cell lines at the RNA and protein levels.

Methods: qPCR was used to quantify VBl-1 mRNA in the following nine human bladder cancer cell lines: UM-UC-3, T24, J82, TCCSUP, RT4, SW780, HT1376, HT1197, and 5637. Western blot analysis was used to verify full length and low molecular weight AR proteins and AR proteins following knockdowns of total AR and VBl-1. Immunofluorescence was used to localize total AR within the cells. CCK8 and caspase 3/7 assays were used to analyze cell viability and apoptosis respectively, after siRNA-mediated depletion of VBl-1. VBl-1 cloning used 3' RACE followed by cloning into TOPO and pcDNA3(+) plasmid. VBl-1 gene activation was assessed through AR dependent promoter-Luciferase transactivation assays.

Results: The tested cell lines expressed varying levels of full-length AR and low molecular weight AR proteins. qPCR quantification also verified that UM-UC-3 and TCCSUP cells had the highest expression of AR, followed by T24 and RT4 with medium expression, SW780, HT1376, and 5637 with low expression. J82 and HT1197 cells did not express full length AR, but expressed small amounts of low molecular weight AR. VBl-1 was expressed in 6 out of the 9 cell lines including: UM-UC-3, T24, J82, TCCSUP, HT1197, and HT1376. Localization of AR appeared to be both nuclear and cytoplasmic in the medium to higher expressing total AR cell lines. Immunofluorescence in VBl-1 overexpressing UM-UC-3 clones showed high levels of AR nuclear

localization. Knockdown of VBl-1 in UM-UC-3, T24, and TCCSUP cells resulted in significant decreases in cell viability by 6 days as a result of apoptosis (in UM-UC-3 and T24 cells). VBl-1 transactivated the androgen promoter-luciferase construct in a dose dependent manner.

Conclusion: These results show, for the first time in bladder cancer, a novel mutated AR variant capable of localizing to the nucleus, promoting AR-dependent gene expression, and affecting tumor cell viability and apoptosis. Targeting low molecular weight AR may provide novel therapeutic approaches for bladder cancer treatment.

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<<22>> MITIGATING EGFR- AND ERK-DEPENDENT RESISTANCE TO ENZALUTAMIDE IN CASTRATION-RESISTANT PROSTATE CANCER

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Background: Androgen receptor (AR) signaling inhibitors (ASI) enzalutamide (enz) and abiraterone acetate (abi) are standard treatments for patients with castration resistant prostate cancer (CRPC). Patients who develop resistance to these therapies have very few options. Epidermal growth factor receptor (EGFR) activity and expression are often upregulated in CRPC, so we explored inhibition of EGFR and its downstream effector ERK in ASI-resistance.

Methods: Human prostate cancer (PCa) cell lines C4, C4-2B, PC-346C, CWR-R1, and 22Rv1 were continuously cultured in enz to induce or increase resistance. PCa cell lines were treated with enz, lapatinib (lap, HER2/EGFR inhibitor), erlotinib (erlo, EGFR inhibitor), dacomitinib (daco, pan-ErbB inhibitor), ulixertinib (ulix, ERK inhibitor), or trametinib (tram, MEK inhibitor). Patient-derived-xenografts (PDX) and organoids were prepared from tumor tissues obtained from metastatic lesions of patients resistant to abi. PCa tumor tissues harvested from patient-derived-xenograft (PDX) mice models were prepped with gentle MACs dissociators (Miltenyi Biotec, Germany). Organoids were collected and treated with DMSO, enzalutamide, erlotinib, or the combination in the presence of DHT. Whole genome sequencing was done at the UC Davis Comprehensive Cancer Center Genomics Core.

Results: Whole genome sequencing revealed that enz-resistant C4-2B and 22Rv1 had elevated expression of genes associated with ErbB signaling when compared to parental lines, including EGFR ligands. Stimulation with these ligands resulted in EGFR (Y1068) and ERK phosphorylation. Hence, we investigated whether EGFR and ERK inhibitors prevented or reduced enz-resistance. In MTTs, erlo and daco reduced viability in combination with enz, but lap did not. Combining erlo with enz reduced the growth of abi-resistant organoids expression high EGFR more than either drug alone. Similarly, combining daco and enz decreased growth for abi-resistant PDX more than either drug alone. Downstream of EGFR activation, erlo and daco, but not lap, reduced EGF-induced ERK phosphorylation. Long term treatment of enz-sensitive C4 cells with enz, created enz-resistant line (C4-Enz) that had novel constitutive ERK phosphorylation not present in parent line (C4-DMSO). We observed that C4-enz cells, similar to parental cells, are still susceptible to the combination of erlo and enz, indicating a method of inhibiting ASI-resistant CRPC. Significantly, only EGFR (not ErbB2/ErbB3) knockdown reduced constitutive ERK phosphorylation in PC-346C but not in 22Rv1. However, ulix and tram could alter 22Rv1 ERK phosphorylation levels. Like the EGFR inhibitors, ulix or tram reduced viability of enz-resistant lines in combination with enz. Combining enz and ulix with either daco or erlo (triple combination) reduced viability even further than either drug alone or in double combination.

Conclusions: Enz-resistance from EGFR ligand upregulation, that induces EGFR phosphorylation (Y1068) and ERK phosphorylation, can be effectively reduced by combining enz and an EGFR inhibitor, such as erlo or daco, that successfully decreases ERK phosphorylation. However, other forms of enz resistance may be attributed to ERK activity and non-genomic AR signaling. Our results suggest that treatment with enz along with an ERK inhibitor like tram or ulix may help reduce these other forms of enz resistance.

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<<23>> EXPRESSION OF ARGINOSUCCINATE SYNTHASE 1 (ASS1) IN LOCALIZED AND METASTATIC PROSTATE CANCER TISSUE

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Background: Arginine is an indispensable amino acid for the synthesis of proteins, nucleotides, polyamines, nitric oxide etc. However, in normal cells, arginine is considered to be a "non-essential" amino acid, since it can be synthesized *de novo* from citrulline via argininosuccinate synthase1 (ASS1), and argininesuccinate liase (ASL). ASS1 is also the rate-limiting enzyme in the pathway converting aspartate to fumarate. However, in >70% of tumor cells, ASS1 expression is suppressed due primarily to promoter methylation, making it the most prevalent metabolic deficiency of cancer. Because ASS1 is silenced in cancer cells, intrinsic arginine production is blocked. Therefore, extrinsic (dietary) arginine, non-essential in non-cancerous human cells, becomes critical to the survival of cancer cells, a condition known as arginine auxotrophy. Given the importance of arginine in cellular processes and it's role as the most consumed amino acids in the inner mass of tumors, it is counter-intuitive that ASS1 is epigenetically suppressed in cancer cells. One possible explanation is that ASS1 diverts aspartate to arginine synthesis from pyrimidine/purine synthesis, which is essential for tumor cells. Overexpression of ASS1 in tumor cells suppress cell growth.

Methods: Two sets of tissues were used for this study. 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 castration resistant prostate cancer (mCRPC) between 1995 and 2013 were obtained from the archives of Mayo Clinic, Rochester, MN. FFPE samples were arranged in tissue microarrays (TMA) and the TMAs sectioned and stained with antibodies to androgen receptor (AR), the cell proliferation marker Ki67 and ASS1. Balb/c mice were left intact (n=6), Correlations between markers and PSA were estimated and tested using the Spearman (nonparametric) correlation. Marker expression was compared between groups using the Kruskal-Wallis test. Analyses were conducted using R, version 3.4.4.

Results: Since two disparate sets of data were used for localized tumors and distant metastases, we did not compare the expression of ASS1 in the two sets; however, immunohistochemistry (IHC) data showed that ASS1 in both sets was mostly cytoplasmic. In the localized tissues, ASS1 levels were significantly higher in normal tissue compared to prostate tumors (p=0.0079). In the tumors, ASS1 was not associated with age, prostate size, race, smoking, BMI, preoperative PSA, surgical margin or clinical stage. However, cancer samples from Gleason 5-7 tumors had significantly higher cytoplasmic ASS1 expression than those from Gleason 9 tumors (P = 0.006). To determine whether ASS1 indeed has a tumor suppressive effect in prostate cancer tissue, we investigated correlation between ASS1, and the proliferation marker Ki67. In cancer samples, Ki67 was negatively correlated with cytoplasmic ASS1 (R= -0.31, p = 0.015). Curiously, statin use increased (p=0.005) while aspirin lowered (p=0.015) the levels of ASS1, but only in non-tumor samples. Since PCa is an androgen-receptor (AR) regulated disease, we also investigated any correlation between AR and ASS1. In the localized tissues, there was a trend towards negative correlation between nuclear AR (active) and

ASS1, and a positive correlation between cytoplasmic AR (inactive) and ASS1, but this correlation was not significant. In the metastatic tissues examined, on the other hand, there was significant negative correlation between ASS1 and nuclear AR (R= -0.35, p=0.016) as well as ASS1 and PSA levels (R= -0.3, p=0.049). Significantly, treatment with chemotherapy following androgen deprivation therapy (ADT), but not ADT alone, restored ASS1 levels (p=0.0022).

Conclusions: Increased levels of ASS1 is associated with normal prostate architecture and lower proliferation. Importantly, it appears that ASS1 is negatively correlated with AR activation, suggesting suppression of ASS1 expression by AR. Interestingly, chemotherapy appears to restore ASS1 levels, perhaps due to a decrease in AR activation. These results indicate that ASS1 may be an effective marker of treatment efficacy in PCa.

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<<24>> OVERCOMING ABCB1-MEDIATED OLAPARIB RESISTANCE IN ADVANCED PROSTATE CANCER

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Background: Despite great progress in the management of advanced, castration-resistant prostate cancer (CRPC), it is estimated that over 29,000 men will lose their lives to this disease in 2018. It is imperative that novel therapies be added for this indication. The recent phase II TOPARP-A study highlighted the potential role of using PARP inhibitors for the treatment of a subset of heavily pre-treated prostate cancer patients harboring DNA-repair defects in their tumors. Although these new findings are exciting, many questions remain regarding the optimal use of these therapies including; 1) whether there is cross-resistance with other approved drugs, 2) where to place PARP inhibitors in the treatment paradigm, and 3) what combinations of currently approved drugs may produce the best effects? The aim of our study was to utilize our labs models of therapeutic resistant CRPC to explore putative cross-resistance with olaparib

Methods: C4-2B based enzalutamide resistant MDVR, abiraterone resistant AbiR, and docetaxel resistant TaxR cells as well as docetaxel resistant DU145 based DU145-DTXR cells were previously described. Cell growth and colony formation assays were used to test response to olaparib and putative combination treatments. Western blots were used to assess expression of PARP, PAR, and ABCB1. Cell compartment fractionation was used to assess chromatin bound PARP.

Results: Our data demonstrate that enzalutamide and docetaxel resistance confer cross-resistance to olaparib. We focused our study on docetaxel mediated cross-resistance as it was the most robust. Our previous studies showed that ABCB1 mediates taxane resistance. We hypothesized it may also mediate olaparib resistance. shRNA-knockdown of ABCB1 re-sensitizes docetaxel resistant cells to olaparib treatment. Small molecule inhibition of ABCB1 using either elacridar or enzalutamide also re-sensitizes docetaxel resistant cells to treatment.

Conclusions: Our findings highlight the potential for cross-resistance with currently used therapeutics and suggest that olaparib combination therapies may yield the highest efficacy.

<<25>> NOVEL GALECTIN-1 INHIBITOR FOR CASTRATION-RESISTANT PROSTATE CANCER

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Background: Patients with advanced prostate cancer (PCa) who are treated with androgen deprivation therapy (ADT) will eventually develop castration-resistant prostate cancer (CRPC). Currently, CRPC is treated with chemotherapy (docetaxel, cabazitaxel) and androgen signaling inhibitors (ASI; enzalutamide, abiraterone acetate), while radiotherapy and immunotherapy are reserved for those resistant to the first two. The duration of efficacy of these treatments is relatively brief; indicating the need for precision medicine. We recently showed that galectin-1 (Gal-1) was highly expressed in CRPC compared to normal prostate and localized PCa. Gal-1 knockdown significantly inhibited CRPC cells' growth, anchorage independent growth, migration and invasion through the suppression of androgen receptor (AR) and Akt signaling. Therefore, Gal-1 is an important target for CRPC therapy. Currently, no Gal-1 inhibitors have been approved for clinical use in patients due to lack of potent, specific and in vivo effective molecules without significant toxicity. We recently developed a novel small molecule inhibitor of Gal-1, LLS30 which demonstrated significant cytotoxic effects in Gal-1 expressing, but not Gal-1 low, CRPC cell lines, and disrupted cell adhesion in high Gal1 cells. LLS30 showed *in vivo* efficacy in both AR positive and AR negative prostate cancer xenograft models without toxicity. LLS30 not only can potentiate the anti-tumor effect of docetaxel to cause regression of tumors but can also effectively inhibit the invasion and metastasis of PCa cells *in vivo*. Taken together, LLS30 is a promising small molecule that warrants further development as a novel and first-in-class therapeutic drug against CRPC. In this study, we further investigate its target specificity and action of mechanism.

Methods: Biotinylated LLS30 was used to pull-down target proteins which were determined by LC-MS/MS. To determine the specificity of LLS30 to Gal-1 vs Gal-3, binding-blocking of FITC-labeled Gal-1 and Gal-3 to Chinese Hamster Ovary (CHO) cells with/without LLS30 was performed. The effect of ABI treatment on Gal-1 localization was investigated in patient derived xenograft (PDX) models. Organoids derived from PDX models established with pre- and post-ABI mCRPC (PR04 and PR10 respectively) were used to study the effect of DOX.

Results: Protein pull-down assay shows the following proteins to have the highest binding to biotinylated LLS30 – PRKDC, GCN1, CSE1L, EPRS, LRPPRC, CAND1, in addition to Gal-1. Binding specificity study showed that LLS30 reduces the binding of CHO cells to Gal-1 but little to Gal-3, indicating LLS30 binds preferentially to Gal-1. To study the effect of ABI treatment on Gal-1 localization in PDX models, PDX xenografts were established from biopsy material obtained from patients with metastatic CRPC before and after treatment with ABI+prednisone by renal capsule xenografting following subcutaneous testosterone pellet implantation in NSG mice. Expansion of sub-renal xenografts was observed 4-6 months after implantation of baseline (n=4) or post-12-week therapy (n=3) biopsy tissue. All models show either innate (pre-ABI) or acquired resistance (post-ABI) to ABI. 3/4 (75%) PDX models from tumors that were not treated with ABI displayed cytoplasmic Gal-1 (score 1-2), while 2/3 (67%) of the ones from tumors of patients who had been treated with ABI expressed nuclear Gal-1 (score 2-3). PR10 expressed high levels of Gal-1, while in PR04 Gal-1 levels were negligible, showing that AR suppresses Gal-1, whereas ABI, similar to ENZA, releases this suppression. Organoids derived from PR04 (low Gal-1) were highly responsive to DOX at 10 nM, whereas organoids derived from PR10 with high Gal-1 showed innate resistance to DOX. These results indicate a direct correlation between Gal-1 expression and DOX resistance.

Conclusions: Our data show that ABI treatment stimulates Gal-1 mRNA levels, thereby indicating that the AR suppresses Gal-1 expression. Gal-1 expression is correlated with DOX resistance. LLS30/DOX combination treatment may serve as potential novel therapeutic approach to treat CRPC patients who have developed resistance to ASI.

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<<26>> METHIONINE ADENOSYLTRANSFERASE 1A (MAT1A) ENHANCES CELL SURVIVAL DURING CHEMOTHERAPY TREATMENT AND MAY BE ASSOCIATED WITH DRUG RESISTANCE IN BLADDER CANCER

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Background: Bladder cancer is among the top ten most common cancers, with about ~380,000 new cases and ~150,000 deaths per year worldwide. The stage of disease at the time of diagnosis is critical for determining patient outcome; the survival rate for cancers found at early stages is greater than 85%. However, once the cancer has reached stages 3 or 4 and has progressed from the bladder to the abdominal cavity or lymph nodes, the 5-year survival rate drops below 50%. Cancer becomes increasingly challenging to treat as it metastasizes and reaches other tissues. Routine standard of care treatment with first line chemotherapeutics such as cisplatin and gemcitabine typically result in tumor resection, however, most cases relapse to develop drug resistance and persist despite initial chemotherapeutic sensitivity. Tumor relapse following chemotherapy treatment has long been a significant challenge towards completely curing cancer.

Methods: We have employed patient-derived xenograft (PDX) models of muscle invasive bladder cancer to profile the transcriptome of drug relapsed tumors in order to investigate underlying mechanisms of drug resistance. Two unique PDX tumor lines were utilized, BL0293 and BL0440, each with sensitivities to cisplatin/gemcitabine combination therapy. RNA sequencing analysis was conducted before and after a 21-day cisplatin/gemcitabine drug treatment regimen to identify differentially expressed genes contributing to tumor relapse.

Results: Methionine adenosyltransferase 1a (*MAT1A*) was identified as one of the top differentially expressed genes when both BL0293 and BL0440 relapsed following drug treatment. Increases in expression were confirmed in chemotherapy treated deidentified bladder cancer patient tissue microarrays (TMAs). *MAT1A* was also found to play an important role in enhancing cancer cell survival during and after chemotherapy treatment *in vitro*. Further, transcriptomic analysis of 5637 cells overexpressing *MAT1A* suggest decreases in cell proliferation as a potential mechanism by which bladder cancer cells can persist despite treatment.

Conclusion: This study implicates *MAT1A* as a key contributor promoting bladder cancer relapse following chemotherapy treatment. As such, *MAT1A* may serve as a potential biomarker for clinical screening of disease progression. Additionally, we suggest decreases in cell proliferation as a potential mechanism by which cancer cells can evade chemotherapy treatment to nonspecific therapies, such as gemcitabine. *Support was provided by NIGMS P41 GM103483 and the Livermore Graduate Scholar Program funded by DOE. This work was conducted under the auspices of the USDOE by LLNL (DE-AC52-07NA27344). IM number: LLNL-POST-688318.*

<<27>> CHARACTERIZATION OF THE TUMOR MICROENVIRONMENT USING SINGLE CELL TRANSCRIPTOMICS OF TRIPLE NEGATIVE BREAST CANCER ALLOGRAFTS TREATED WITH DOXORUBICIN

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The contribution of stromal populations' effects on drug response in primary tumors remains unclear. Doxorubicin (Dox) is a common chemotherapeutic used to treat triple negative breast cancer (TNBC) that

inhibits cancer proliferation by intercalating into DNA and preventing topoisomerase II activity. However, disease progression will occur in an estimated 20–30% of patients with early-stage disease following adjuvant therapy. In this study, we used an allograft mouse model of TNBC to investigate the mechanism of Dox drug resistance. We employed mouse derived 4T1 TNBC cells to generate tumors in immunocompetent BALB/c mice and analyzed tumors after 8 days of Dox treatment. Interestingly, 4T1 tumors exhibited either resistant or sensitive responses upon exposure to Dox treatment. We performed single-cell RNA sequencing (scRNA-seq), a technology used to examine gene expression in individual cells, on 4T1 tumors to determine the contribution of various stromal cell types to Dox resistance and diversity of unique stromal cell populations. scRNA-seq data showed differences in the abundance of T-cells and myeloid-derived suppressor cells (MDSC) between resistant and sensitive tumor groups. Further, scRNA-seq data suggest an increase in T-cell abundance in Dox-sensitive tumors compared to resistant tumors. These results were further confirmed using flow cytometry, showing resistant tumors had significantly less CD4 and CD8 T-cells compared to sensitive tumors, suggesting that T-cells may contribute to chemotherapy responses in TNBCs.

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<<28>> ELUCIDATING THE MECHANISM OF ACTION FOR HEXAMETHYLENE AMILORIDE IN THE TREATMENT OF BREAST CANCER

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Breast cancer afflicts 1 in 4 women worldwide, and is the second leading cause of death for US women behind lung cancer. While breast cancer outcomes have improved in recent years, effective treatment of metastatic disease remains a challenge. Conventional therapeutic agents, while effective to a certain extent, are incapable of fully eliminating heterogenous tumor cell populations responsible for recurrence. We have previously reported that hexamethylene amiloride (HMA), a derivative of the diuretic amiloride, efficiently kills tumor cells but not non-transformed cells. The objective of this project is to begin to unravel mechanisms underlying HMA cytotoxicity toward therapy-resistant tumor cells. Cell viability assays demonstrate that HMA is cytotoxic toward drug-resistant breast cancer cell subpopulations, while microscopic assays strongly point to a necrotic cell death mechanism initiated by HMA-induced lysosomal membrane permeabilization. Though HMA harbors particularly attractive qualities, further optimization will be required to improve drug potency and pharmacokinetic properties. Once optimized, we envision that an HMA-related molecule could serve as a secondary agent administered to patients following primary treatment to eradicate any remaining treatment-resistant tumor cell populations.

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<<29>> IMPACT OF THE ARYL HYDROCARBON RECEPTOR SIGNALING PATHWAY ON MAMMARY TUMORIGENESIS

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Background: The aryl hydrocarbon receptor (AhR) is known for mediating the toxicity of environmental pollutants such as dioxins and numerous dioxin-like compounds. Due to the widespread occurrence in our environment and the high toxic potential, these contaminants are of concern to promote breast cancer. Several studies have shown that the AhR is critically involved in mediating defects of the mammary gland differentiation

and suppresses mammary gland development. More recently it has been found that the AhR may also act as a critical receptor protein in tumor promotion independent from exogenous ligands, which is based on its role in immune tolerance and increased survival in cancer cells. Consequently, the AhR may serve as an attractive target for new drugs in breast cancer therapy. AhR's action is restricted by a specific repressor protein, the AhR Repressor (AhRR). Interestingly, a recent report found that breast cancer patients who had low AhRR expression also had shorter metastasis-free survival and identified AhRR as an independent prognostic factor. While AhRR effectively blocks AhR, the role of AhRR as a tumor suppressor gene is only poorly understood. We hypothesize that AhRR will oppose AhR-mediated mammary tumorigenesis.

Results: We established a transgenic mouse (AhRR Tg mice) that overexpresses AhRR and discovered that these mice were protected from tumor promoting effects induced by dioxin. To test the tumor-suppressive action of AhRR in vivo, we used a syngeneic murine tumor model in which E0771 mammary tumor cells are engrafted in the mammary fat pad. Results indicate a significantly suppressed tumor growth of E0771 cells in AhRR Tg mice compared to control B6 mice. Tumor growth was enhanced in dioxin-treated wt mice, as expected, but was significantly suppressed in AhRR Tg mice, supporting our hypothesis. Moving forward, we plan to examine the impact of AhRR overexpression in other mammary tumor models. The polyoma middle T antigen (PyMT) mouse model is a well-accepted model of ER-negative, metastatic breast cancer. Our data show, that the expression of AhR increases significantly in mammary tumors during progression in PyMT mice. In contrast, the expression of AhRR decreases. Furthermore, expression of inflammatory markers (e.g. COX-2 and C/EBPβ) increases during tumor progression. The preliminary results indicate that the PyMT mouse is a suitable model to study the role of AhR and AhRR in breast tumorigenesis since it reflects a similar expression pattern found in human breast cancers.

Conclusion: Our data indicate that AhRR restricts AhR-dependent expression of pro-inflammatory cytokines and acute toxicity. We also show that the AhRR represses the PKA-C/EBPβ inflammatory axis, induced by AhR activation, supporting its role as a tumor suppressor. Furthermore, AhRR opposes AhR-driven tumor cell survival. In summary the results show that AhRR suppresses mammary tumor cell growth in vivo and regulates genes involved in inflammation and apoptosis. The results will help us to understand AhRR's function as a tumor suppressor gene and the potential biomarkers of mammary tumorigenesis mediated by AhR and environmental toxicants.

<<30>> INTRATUMOR HETEROGENEITY IN GASTRIC ADENOCARCINOMAS FROM LATINOS

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Gastric (stomach) cancer (GC) is the 2nd leading cause of cancer-related death worldwide. It is diagnosed in 25,000 Americans each year, with Latinos twice as likely to succumb as Whites. Treatment is currently limited to few molecularly-guided therapies but TCGA data shows that 70% of GC patients have a mutation in a gene targetable with existing drugs. Significant spatial mutational intratumor heterogeneity (ITH) has been identified in a variety of tumor types to date, although a GC ITH study has yet to be published. ITH is an important consideration for personalized therapy. Driver gene mutations are frequently found to be non-clonal, a crucial factor when assessing effective druggability. The goal of this study was to examine GC ITH in Latino samples using multi-regional sequencing (MSEQ). Two to five tumor biopsies and adjacent normal tissue were obtained from 33 Latino patients, totaling 120 tumor (T) biopsies and 33 normal (N) samples. DNA was extracted from the tissues, and the coding regions of 762 cancer-related genes were sequenced using Agilent target enrichment and Illumina sequencing. Somatic mutations were called in each biopsy using joint analysis of all T and N sequence data for each patient, and cancer cell fraction (CCF) was estimated for each mutation in each biopsy. Purity and ploidy were estimated and copy number variation (CNV) across the genome was called, for each biopsy. Somatic mutations and copy number changes were analyzed for clonality in each patient. We found a high degree of heterogeneity, both intratumor and interpatient, with the fraction of functional somatic mutations that are *clonal* ranging from 0 to 68%, the fraction *private* to one tumor sample ranging from 32% to

100%, and the fraction *shared* between multiple but not all samples ranging from 0 to 42%. For 10 of the 33 samples there was at least one gene, containing a clonal functional mutation, for which there is a FDA approved targeted therapy. In summary, our study is the first to assess ITH in GC. Our results are important to understand the genetic diversity and clonal architecture of these tumors and to improve molecular diagnostics.

<<31>> FEASIBILITY STUDY TO IDENTIFY AND COLLECT DATA ON ENVIRONMENTAL RISK FACTORS FROM HISPANIC WOMEN DIAGNOSED WITH LUNG CANCER

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Introduction: Risk factors for lung cancer among nonsmokers are not well understood and prior studies of this topic have produced inconsistent results. In addition, identifying a large group of lung cancer patients who are nonsmokers is difficult, particularly because population-based cancer registries do not collect smoking history. The purpose of this pilot project, funded by the NIEHS Core Center for Environmental Health Sciences at UC Davis, is to assess the feasibility of using the cancer registry to identify lung cancer patients who are likely nonsmokers, and to assess the feasibility of using a telephone interview to identify patients' exposure to environmental risk factors.

Methods: Patients will be identified through the Cancer Registry of Greater California, a SEER registry that also is a component of the California Cancer Registry. To select a group of lung cancer patients who are more likely to be nonsmokers, we will recruit female Hispanic patients recently diagnosed with adenocarcinoma of the lung. Smoking prevalence among Hispanic women is the lowest among all ethnic groups, and lung cancers diagnosed among nonsmokers are more likely to be categorized as adenocarcinomas. Information on residential and occupational history as well as exposure to probable risk factors for lung cancer including smoking, environmental tobacco smoke, and household exposures will be collected using a phone survey. The survey also will be used to gather the same information from friend controls identified by the study participants. A total of 20 cases and 20 control subjects will be recruited for this feasibility study. Prior to contacting lung cancer patients, the questionnaire will be pre-tested on a focus group composed of female Hispanic colon cancer survivors.

Results: Due to delays in funding, data collection for this study is just beginning. The survey has been developed and approved by all three responsible IRBs (PHI, UCD, CPHS). Focus groups will be held in October 2019, and surveys of lung cancer patients will be conducted in October and November.

Discussion: We expect that this pilot study will provide preliminary data to support larger studies of environmental factors that increase cancer risk. In 2019, we were asked to contribute to an NIH grant proposal led by Dr. Luis Carvajal-Carmona to study arsenic and lung cancer. In addition, since the registry geocodes patient addresses at diagnosis, this project may lead to studies that evaluate geographic distribution of cancer patients and environmental risk factors.

<<32>> RECENT SMOKING-ATTRIBUTABLE FRACTIONS OF CANCER DEATHS AND DISPARITIES ACROSS RACE/ETHNIC, INCOME, EDUCATION AND TEMPORAL STRATA IN U.S. MEN

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Significance**:** Cumulative smoke damage's (smoke load's) nearly exclusive roles in lung, and some non-lung (all sites but lung), cancer rate disparities are clear. But smoke load's potential contributions to recent national: temporal; race-ethnic; education, and income-related non-lung cancer mortality disparities have not been studied. So, I studied non-lung cancer/smoke load associations across such disparities in nationally representative United States men aged 25+ years.

Methods**:** I used lung cancer death rates as a smoke load biomarker (predictor). I studied nationally representative U.S. non-lung/lung cancer death age-adjusted rate associations from 2003-2011 using published rates by: a) year from the National Center For Health Statistics (NCHS) (with known biases due to differential census undercounts and proxy-reported decedent age and race), and b) income-, education-, and race-ethnicity per the National Longitudinal Mortality [cohort] Study which lacked those NCHS rates' biases. I used Stata regressions.

Results**:** U.S. non-lung cancer deaths/100,000/year rates studied ranged, respectively, from: 138 to 213 (for incomes under 100% versus over 600% of poverty level, respectively); 112 to 255 (for Asian/Pacific Islanders versus American Indian/Alaska Natives, respectively), and 89 to 111 for 2011 versus 2003, nationally. Non-lung/lung cancer rate slopes were 1.2 (95% confidence interval 0.89-1.50, R-squared 0.97) across race-ethnic strata, 0.98 (95% confidence interval 0.70-1.25, R-squared 0.96) across income strata, 0.95 ((95% confidence interval -0.48-2.4), R-squared=0.80)) across education, and, across the years 2003-2011 with Cochrane-Orcutt adjustment for possible autocorrelation, 0.98 ((0.64 - 1.32), R-squared=0.88) for all men, 0.84 ((0.66 - 1.01), and R-squared=0.95) for non-Hispanic White men, and 1.53 ((1.47 - 1.59), and R-squared=1.0) for non-Hispanic African American men.

Conclusion**:** Very strong, consistent, dose-response, and biologically plausible, so possibly causal, associations between smoke load and non-lung death rates were seen across the nationally representative disparities and men studied. The associations suggest that smoke load differences may account for 97% of the race-ethnic disparities, 96% of the income-related disparities, and nearly 100% of the temporal disparities studied. To reduce cancer death rates and disparities in United States men, nearly exclusively focusing on reducing smoke exposures may be merited.

<<33>> THE CANCER CARE NETWORK CLINICAL TRIALS PROGRAM: RISING FROM THE CAMP FIRE ASHES

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Background: The UC Davis Health Cancer Care Network (CCN) in Sacramento improves quality through partnerships with community cancer centers and the UC Davis Comprehensive Cancer Center (UCDCCC). The UCDCCC, as an NCI Lead Academic Participating Site (LAPS) grant recipient, lists Adventist Health Rideout Cancer Center (RCC) in Marysville (42 miles north of Sacramento) as a component. The Adventist Health Feather River Cancer Center (FRCC) and the town of Paradise were devastated by the 2018 Camp Fire, forcing FRCC's relocation to the city of Chico (49 miles north of Marysville). FRCC was forced to disband its local IRB and unable to continue clinical trials research operations during the aftermath of this natural disaster. The CCN established an affiliation with the FRCC in April 2019. Future plans include establishing an IRB agreement and adding FRCC as a LAPS component. The CCN identified strategies to facilitate the participation of FRCC patients in clinical trials.

Methods: The CCN identified 13 NCTN clinical trials with 34 enrolled patients that were in need of appropriate research oversight. Four of these trials were previously never activated at the UCDCCC or its affiliates. CCN staff engaged leaders at the various institutions involved: Quality Assurance (QA) Managers at each NCTN research base, the CIRB, the local IRB, the CTSU, and other leaders within UC Davis and Adventist Health.

Results: Stakeholders acknowledged the unusual and urgent nature of our requests and questions, while contributing to the development of a plan allowing patients to continue clinical trial participation. QA managers approved a plan transferring patients to the RCC, allowing research staff to collect and submit data while patients continue receiving care closer to home. Together we developed a notification letter to inform patients of this plan.

Conclusion: The relocation of facilities and patients brought rare challenges while conducting clinical research in rural communities. We learned that the cooperation and flexibility of all parties involved was crucial in supporting the continued care for FRCCs clinical trial patients and research contributions

<<34>> SYMPTOMS AND MASK USE REPORTED IN THE B-SAFE PREGNANCY COHORT TO EXAMINE WILDFIRE EXPOSURE HEALTH IMPACTS

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Background/Aims: In the past two years, multiple wildfires of unprecedented devastation ravaged Northern California, hitting urban areas with more fatalities, evacuations, and structures destroyed than ever before. Thick smoke plumes and the highest $PM_{2.5}$ concentrations ever recorded blanketed large metropolitan areas and affected millions, including ~100,000 pregnant women. Combined exposures to contaminants and emotional stress from these urban wildfires could have serious long-term developmental consequences if delivered during critical periods in pregnancy.

The B-SAFE (Bio-Specimen Assessment of Fire Effects) study enrolls women pregnant during wildfires and their children, collects biospecimens and survey information that will be used to understand exposures, mechanistic responses, and health impacts of gestational wildfire exposure.

Methods: Women 18+ years of age who were pregnant and living in Northern California during 2017 wildfires were recruited through local media and social media campaigns. Biospecimens and information were collected in-person pregnancy, delivery, and postnatal visits. Women completed online surveys about their wildfire experience.

Results: Of the 172 participating mothers, most were white 84(%), college educated (77%), married (89%), and enrolled postnatally (145%). Of the first 149 B-SAFE mothers taking the 2017 wildfire survey, 104 (70%) reported having symptoms. The most commonly reported maternal symptom was stress/anxiety, which affected 48%; ~20% remained affected up to a year after the fires. Itchy/irritated eyes and cough were reported in over 30% initially, but dropped steeply after the first month; trouble sleeping was reported for 15-22% in the first several months. 'Sore throat' was the most commonly reported 'other symptom.' Most mothers (80%) reported wearing masks; most (84%) were N95. Respiratory symptoms were reported for children primarily in the first month, and were higher for families who experienced higher particulate matter exposure and for those who evacuated. Reported symptoms were also somewhat higher among those who used masks.

Conclusions: This cohort and biorepository will expand to include mothers pregnant during the 2018 Camp Fire and will provide a resource for future studies to understand and minimize the biological and developmental effects of wildfires, as they increase in number, duration, and intensity.

<<35>> UPPER EXTREMITY DEEP VEIN THROMBOSIS IN ACUTE LEUKEMIA AND NON-HODGKIN'S LYMPHOMA: ANALYSIS OF THE CALIFORNIA CANCER REGISTRY

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Background: Venous thromboembolism (VTE) is a known complication in patients with acute myeloid leukemia (AML), acute lymphoid leukemia (ALL) and non-Hodgkin's lymphoma (NHL). However, the cumulative incidence, risk factors, rate of subsequent VTE and impact on mortality of upper extremity deep vein thrombosis (UE DVT) in these diseases is not well-described.

Methods: Using the California Cancer Registry, we identified patients with a first primary diagnosis of AML, ALL and NHL from 2005-2014 and linked these patients with the statewide hospitalization and emergency department databases to identify an incident UE DVT event using specific ICD-9-CM codes. Patients with VTE prior to or at the time of malignancy diagnosis or who were not treated with chemotherapy were excluded.

We determined the cumulative incidence of first UE DVT, adjusted for the competing risk of death. We also examined the cumulative incidence of subsequent VTE (UE DVT, lower extremity deep vein thrombosis (LE DVT) and pulmonary embolism (PE)) and major bleeding after incident UE DVT. Using Cox proportional hazards regression models, stratified by tumor type and adjusted for other prognostic covariates including sex, race/ethnicity, age at diagnosis, neighborhood, sociodemographic status and central venous catheter (CVC) placement, we identified risk factors for development of incident UE DVT, the effect of incident UE DVT on PE and/or LE DVT development, and impact of incident UE DVT on cancer specific survival. The association of CVC placement with incident UE DVT was not assessed in acute leukemia patients, as all who undergo treatment were assumed to have a CVC. Results are presented as adjusted hazard ratios (HR) and 95% confidence intervals (CI).

Results: Among 37,282 patients included in this analysis, 6,213 had AML, 3,730 had ALL and 27,339 had NHL. The 3- and 12-month cumulative incidence of UE DVT was 2.6% and 3.6% for AML, 2.1% and 3% for ALL and 1.0% and 1.6% for NHL respectively. Most (56-64%) incident UE DVT events occurred within the first 3 months of malignancy diagnosis. African Americans (HR 1.66; CI 1.22-2.28) and Hispanics (HR 1.35; CI 1.10-1.66) with NHL had an increased risk of incident UE DVT compared to non-Hispanics Whites. NHL patients with a CVC had over a 2-fold increased risk of incident UE DVT (HR 2.05; CI 1.68-2.51) compared to those without a CVC. UE DVT was a risk factor for development of PE or LE DVT in ALL (HR 2.53; CI 1.29-4.95) and NHL (HR 1.63; CI 1.11-2.39) but not in AML. The 12-month cumulative incidence of subsequent VTE after an incident UE DVT diagnosis was 6.4% for AML, 12.0% for ALL and 7.6% for NHL. 46-58% of subsequent VTEs occurred within the first 3 months of incident UE DVT diagnosis. The majority of subsequent VTEs were UE DVT which had a 12-month cumulative incidence of 4.6% for AML, 6.6% for ALL and 4.0% for NHL. The 12-month cumulative incidence of subsequent LE DVT was 1.3% for AML, 1.6% for ALL and 1.9% for NHL. The 12-month cumulative incidence of subsequent PE was 0.4% for AML, 4.1% for ALL and 1.8% for NHL. The 12-month cumulative incidence of major bleeding after an UE DVT diagnosis was 29% for AML, 29% for ALL and 20% for NHL. Common major bleeding events included gastrointestinal (GI) bleeds, epistaxis and intracranial hemorrhage. GI bleeding was the most common major bleeding event among all three malignancies (14.2% in AML, 9.6% in ALL and 12.4% in NHL). The rate of intracranial hemorrhage was 6% in AML, 3.5% in ALL and 1.7% in NHL. A diagnosis of incident UE DVT was associated with an increased risk of cancer-specific mortality in all three malignancies (HR 1.38; CI 1.16-1.65 in AML, HR 2.16; CI 1.66-2.82 in ALL, HR 2.38; CI 2.06-2.75 in NHL).

Conclusions: UE DVT is an important complication among patients with AML, ALL and NHL, with the majority of UE DVT events occurring within the first 3 months of diagnosis. The most common VTE event after an index UE DVT was another UE DVT, although patients also had subsequent PE and LE DVT. UE DVT was a risk factor for development of PE or LE DVT in ALL and NHL, but not in AML. Major bleeding after an UE DVT was high in all three malignancies (>20%), with GI bleeds being the most common; the potential contribution of anticoagulation to bleeding cannot be determined by this data. UE DVT in patients with AML, ALL and NHL is associated with increased risk of mortality.

<<36>> A MULTI-LEVEL APPROACH TO ACCELERATING THE HUMAN PAPILLOMAVIRUS (HPV) VACCINE AT A RURAL CLINIC FOR NATIVE AND NON-NATIVE YOUTH

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Accelerating the uptake of Human Papillomavirus (HPV) vaccinations is a priority for cancer prevention and an issue for mitigating cancer health disparities particularly among rural youth, both Native American and non-Native. The rate of HPV vaccinations for rural and Native adolescents is markedly lower than urban adolescents. Based on a Memorandum of Collaboration between the UC Davis Comprehensive Cancer Center and Northern Valley Indian Health (NVIH), a tribal health organization serving rural youth; funding from the National Cancer Institute; and the principles of community-based participatory research, we developed a multi-level approach to accelerate the HPV vaccination rates at the NVIH rural clinic in Willows, CA. Ultimately, the goal is to raise the HPV vaccination rates among patients ages 11-17 from the current 27% at this clinic to the Healthy People 2020 goal of 80%.

Our presentation documents a year's relationship-building that includes the intentional input and promising data from multiple levels for launching an accelerated HPV vaccination program, exemplifying the collaboration

between NVIH and a NCI Comprehensive Cancer Center. Starting with community outreach and engagement, our multiple levels included provider and staff trainings; and parent workshops. We began by surveying 12 community members on their HPV vaccination knowledge, attitudes, and behaviors and learned that they had low knowledge of the HPV vaccine and stressed the importance of educating both the community as well as parents. We followed with training of 26 clinic providers and 44 staff (participants were from all four of NVIH's medical clinics). Pre-tests were administered prior to the training and post-tests administered four months later. The training content had 3 objectives: (1) explaining the importance of HPV vaccinations and the rationale for vaccinating at ages 11-12; (2) providing an effective recommendation by clinicians; and (3) providing support to families to decide in favor of HPV vaccination. While there was attrition from pre to post tests, we achieved significant quantitative realignment of the rank order of HPV vaccination (from 3rd to most important) over other vaccinations and increased confidence in their ability to make a strong HPV vaccination recommendation (14% and 6% respectively). Interviews from parents provided insights on their perspectives of HPV vaccination that should be incorporated. Our next steps will be to apply these findings into a multi-pronged HPV vaccination intervention program for rural Native and non-Native adolescents.

<<37>> EVALUATION OF "*FOCUS ON HBV*" THROUGH HALO'S ACADEMY FOR MEDICAL ASSISTANTS

Moon S. Chen, Jr., Mary Pat Pauly, Amy Beste-Fong, George Yang, Duke LeTran, Alexandra Gori, Kit W Tam, Ian Johnson

Hepatitis B (HBV)-linked liver cancer is perhaps the most glaring of the cancer health disparities confronting Asian Americans. Asian Americans are up to 13 times more likely to develop liver cancer, due to chronic HBV infections than any other U.S. population. However, focusing on HBV is not "usual care". Targeting prevention through interrupting perinatal transmission, administrating the birth dose of HBV vaccinations, vaccinating youth, and testing of adults at-risk and linking individuals care reflects evidence-based best practices to mitigate this principal risk factor for the world's second deadliest cancer, liver cancer, that disproportionately affects Asian Americans.

To date though, few Federally Qualified Health Centers or their Look-Alikes, have addressed HBV among their Asian American patients. With funding from the Bristol-Meyers Squibb Foundation and in collaboration with the Health and Life Organization (HALO), the largest healthcare provider to SE Asians in Sacramento County, UC Davis initiated a training session for HALO's medical assistants on June 15, 2019 as part of a systematic approach.

The context, approach, results, evaluative feedback, conclusions, and next steps are presented in the poster. With respect to context, the goals of the training were to lessen the burden of HALO's providers through enhancing compatibility with best practice and extending their medical assistants' skills. The approach was a three-hour interactive session with content provided by nursing, hepatological, cultural, and disparities experts. Post-test versus pre-test changes and evaluative feedback suggests that the Academy was effective in equipping medical assistants for their new roles in HBV prevention and control.

<<38>> CANCER CARE DELIVERY IN A COMPLEX SOCIOTECHNICAL ECOSYSTEM: COMMUNICATION CHALLENGES AND OPPORTUNITIES

Shin-Ping Tu

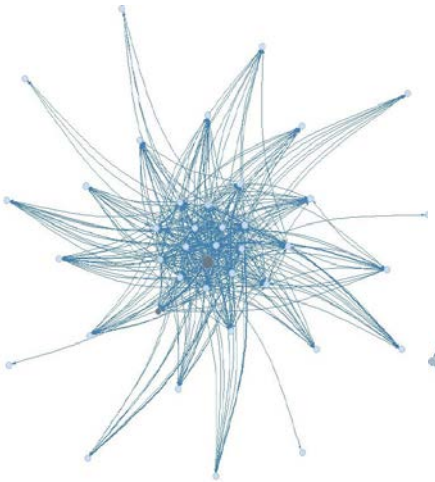
Background: Despite interest in teams, the literature indicates that we know less than expected about what makes teamwork effective in healthcare practice. Effective communication serves as the foundation of high performing teams and increasing electronic health records (EHRs) adoption has changed our healthcare delivery landscape to a human-technological ecosystem. While EHRs have many potential benefits, research suggests that distributed team membership and computer-mediated communication present significant challenges to healthcare delivery. Cancer continues to rank as the second leading cause of mortality in the US and experts have highlighted the urgent need for cancer communication and informatics research to support healthcare professionals (HCPs), patients and caregivers in our human-technological healthcare delivery ecosystem.

Purpose: Apply communication network theories and social network analysis (SNA) to examine EHR-based communication networks among HCPs.

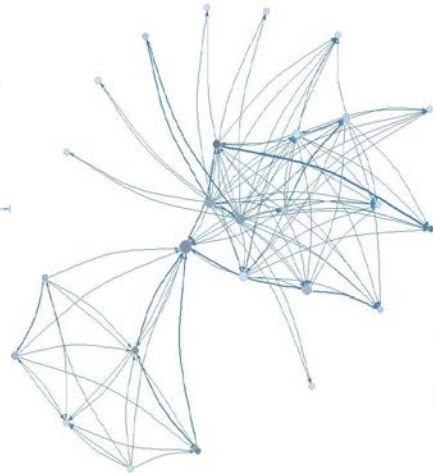
Methods: We randomly selected 100 surgical colorectal cancer patients, then extracted detailed EHR access-log data to create a chronological dataset of HCPs' access to the patients' medical records. Access events were categorized as sending (i.e., documenting) information into or receiving (i.e., reviewing) information from the EHR system. Using the time-stamped access events, we constructed an EHR-based communication network for each patient's cancer care team by assigning a link from a source HCP to a destination HCP using the inverse of the average time between each of the source's send events and, corresponding to each send event, the destination's earliest subsequent receive event.

Results: Our study's 100 EHR communication networks exhibited substantial variations in size (range = 8 to 440 HCPs, mean = 125 HCPs) and structural characteristics. For example, the coefficients of variation for four network centralization measures (i.e., out-degree, in-degree, closeness, and betweenness centralization) are 1.49, 1.49, 1.41, and 0.24 across the 100 networks. We visualized three networks in the size range of 20 to 60 HCPs that represent the maximum variations in closeness and betweenness centralization as illustrated.

1A. EHR Communication Network with



1B. EHR Communication Network with



1C. EHR Communication Network with Low Closeness & Betweenness

Discussion: According to communication network theories, network structural properties will affect EHR-based communication and cancer care team effectiveness. As changes in time, space, and virtual experiences continue to intensify, and affect how HCPs communicate and process information, Monge and Contractor's call for understanding networks of connections and information flow is urgently needed in the healthcare delivery arena.

FRIDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>> ACCELERATING THERAPEUTICS FOR OPPORTUNITIES IN MEDICINE

Brian Bennion[1], Izumi Hinkson[2], ATOM team members

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[2]Frederick National Laboratory for Cancer Research, Frederick, MD

Preclinical drug discovery takes on average five and a half years and accounts for about a third of the cost of drug development. It is typically a slow, sequential process where millions of molecules are screened, thousands are made, and most fail. Only about 10% of drugs entering Phase I trials meet clinical success, and the development of a new drug ultimately costs over US$2 billion. The cost of drug discovery in time and resources is unsustainable for both patients and pharma, especially in small markets. Accelerating Therapeutics for Opportunities in Medicine (ATOM) is a public-private partnership integrating high-performance computing, diverse data, and emerging biotechnologies to create a new platform for drug discovery. ATOM is developing and validating a preclinical drug discovery platform that simultaneously optimizes ADME, toxicity, protein-ligand interactions, systems level models, molecular design, and compound generation. This platform will be made broadly available to the scientific community as a shared resource to accelerate drug discovery. Early results from a pilot study suggest that machine learning methods can predict novel compounds that specifically inhibit kinases important in cancer. Pilot projects of increasing complexity will lead to a proof-of-concept project on a selected cancer target, with lead compounds generated and optimized to a defined human therapeutic window.

We thank Livermore Computing for computational resources.

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<<2>> HYBRID PLASMONIC BIOMATERIAL NANOFILTER SCAFFOLD FOR CANCER EV DIAGNOSTICS BASED ON SURFACE-ENHANCED RAMAN SCATTERING (SERS)

Hanna J Koster[1], Tatu Rojalin[1], Juanjuan Liu[2], Sebastian Wachsmann Hogiu[2], Randy P Carney[1]

[1]Department of Biomedical Engineering, University of California, Davis
[2]Department of Bioengineering, McGill University

There is a dire need to develop sensitive and specific, non- or minimally invasive, cost-effective early detection methodologies for cancer. All cells shed nano-sized packages called extracellular vesicles (EVs) which have recently been shown to play an important role in cell-to-cell communication. However, this pathway can be hijacked by cancer cells and used to circulate tumor-derived EVs that aid in the spread and metastasis of the cancers. These tumor EVs make an attractive option for diagnostics and progression of cancer through biomarkers present on the membrane surfaces. Their rapid isolation and identification are of great interest for adoption into liquid biopsy platforms, since they may represent a snapshot of the tumor state. To study these membrane compounds, we have elected to use surface-enhanced Raman spectroscopy (SERS) for a plasmonic-based detection system. Global chemical compositions can be identified and used to create a next generation liquid biopsy diagnostic platform. To accomplish this, we investigated a new hybrid nanoplasmonic scaffold comprised of a microscale biosilicate substrate embedded with metal silver nanoparticles (AgNPs) for surface-enhanced Raman scattering analysis of ovarian cancer (OvCa) EVs. These substrates are rapidly and inexpensively produced without any complex equipment or lithography. EVs were isolated from different serum sources and incubated on the substrate then interrogated with a laser. The spectra were then compared using principle component analysis (PCA) to tease out the spectral variation and straify the samples into cancerous and noncancerous populations.

<<3>> A RELIABLE LC-MS/MS METHOD FOR THE QUANTIFICATION OF NATURAL AMINO ACIDS: METHOD VALIDATION AND APPLICATION TO STUDIES ON AMINO ACID METABOLISM IN CARCINOMA CELLS AND DURING TUMOR PROGRESSION

Zhenzhen Liu, Mei-Juan Tu, Chao Zhang, Joseph L. Jilek, Qian-Yu Zhang, Ai-Ming Yu

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A simple and fast LC-MS/MS method was developed and validated for the quantification of 20 proteinogenic L-amino acids (AAs) in cancer cells and mouse plasma. Chromatographic separation was achieved on an Intrada Amino Acid column within 13 min via gradient elution with an aqueous solution containing 100 mM ammonium formate and an organic mobile phase containing acetonitrile, water and formic acid (*v*: *v*: *v* = 95: 5: 0.3), at the flow rate of 0.6 mL/min. Individual AA and corresponding stable-isotope-labeled AA internal standards were analyzed by multiple reaction monitoring (MRM) in positive ion mode under optimized conditions. Method validation consisted of linearity, sensitivity, accuracy and precision, recovery, matrix effect, and stability, and the results demonstrated this method as a specific, accurate, and reliable assay. This LC-MS/MS method was thus utilized to: 1) investigate the roles of microRNAs in the control of AA metabolism/transport/homeostasis in various types of cancer cells; 2) examine the dynamics of individual plasma AAs during tumor progression in an orthotropic hepatocellular carcinoma (HCC) xenograft mouse model. The results indicate that miR-328-3p selectively decreases the levels of both intracellular and extracellular arginine in Hep3B cells. Furthermore, our studies reveal a significantly lower Arg concentration as well as higher Ala and Thr levels during HCC progression. These findings shall improve our understanding of new factors behind cancer cell metabolism and development of new remedies for uncontrolled tumor metabolism and progression.

Acknowledgements: This study was supported by National Cancer Institute (grant No. R01CA225958) and National Institute of General Medical Sciences (R01GM113888), National Institutes of Health.

<<4>> DISCOVERY OF A NOVEL FLUORESCENT-ACTIVATING PEPTIDE THAT BINDS TO THE CFA/1 FIMBRIAE OF THE BACTERIA OR CANCER CELLS THROUGH THE USE OF A ONE BEAD ONE COMPOUND (OBOC) TECHNOLOGY

Aman Singla, Shabnam Jafari, Kit S Lam

Department of Biochemistry and Molecular Medicine, University of California Davis, Sacramento, CA 95817

CfA/1, an adhesion pili presents on *E. coli*, plays an important role in intestinal colonization and eventual diarrheal disease. Despite its harmful effects, the ability to precisely identify its location, in a cost-effective and fast way has remained a significant endeavor. Here we report a high-throughput method that allows for synthesizing and screening of millions of unique peptides to discover novel fluorescent-activating peptides that bind to the CFA/1 fimbriae of the bacteria or cell surface receptors of cancer cells. These fluorescent peptides, not only can be used as fluorescent sensor to detect bacteria or circulating cancer cells, but can also be used as targeting agents for drug delivery against these target cells. Total of six OBOC linear and cyclic combinatorial peptide libraries with a molecular rotor dye, malachite green (MG), coupled to the amino group on the side chain of lysine, are being synthesized and will be screened against E. coli or live cancer cells for fluorescent activation under a confocal microscope. Once identified, these peptides will be resynthesized for confirmation of fluorescent activation and targeting properties.

<<5>> TWO-TIERED PLATFORM FOR SEQUENCE-SPECIFIC IDENTIFICATION OF NUCLEIC ACID BIOMARKERS IN COMPLEX BIOLOGICAL FLUIDS

Mashari Alangari, Jovana Veselinovic, Yuanhui Li, Juan Manuel Artés, Zimple Matharu, Erkin Seker, Joshua Hihath

Gene variants can lead to a variety of potentially harmful effects in developing diseases. And, harmful variants in some specific segments of DNA are associated with an increased risk of developing cancer. Recent advances in point-of-care diagnostics have led to the development of high-performance electrical sensors that can provide fast measurements with low cost and multiplexing capabilities. However, detection in complex

environments is still challenging due to the non-specific adsorption of proteins that may foul the sensor surface leading to signal attenuation. Therefore, nucleic acid purification from biological samples is often a crucial, yet a laborious initial step. In general, a simple and reliable approach for base mismatch detection is yet to be achieved. To address these challenges, we present an approach for a biosensor that consists of two stages for mismatch detection in complex environment with simple purification process occurs in the first stage then the second stage investigates at a molecular level the target's sequence using single molecule break junction (SMBJ) technique. The first stage involves a nanostructured electrode, where the electrode morphology has been demonstrated to be biofouling resilient. This coating enables both detection of specific targets in a complex biological sample and their subsequent purification using electrochemical methods. The morphology of the electrodes allows small molecules to pass and participate in the bio-electrochemical reaction happening at the electrode surface. Nanoporous gold (np-Au) electrodes can be modified with a DNA capture probe which enables sensitive detection and capture of complementary DNA or RNA targets in the presence of complex media (blood). The surface-bound DNA:DNA or RNA:DNA can then be released by electrochemically cleaving the thiol-gold linkage, eluting the hybrids from nanoporous matrix for further analysis. Complementary to the electrochemical screening approach, single molecule conductance measurements can provide a molecular insight that is unavailable using electrochemical methods. The single-molecule break junction (SMBJ) system employs a movable, nanostructured electrode tip which makes direct contact to a gold substrate. In these measurements, charge transports between the electrodes through a single bridged-molecule. The magnitude of the current passing through the molecule will change drastically compared to tunneling gap. Here, the eluted sample from the first stage can be investigated using SMBJ which can differentiate between perfectly matched vs mutated targets (3-base mismatch). Our results show the difference in conductance values between perfect and mismatch targets in complex media. The advantages of combining these two approaches offer the ability of detection of single-nucleotide polymorphisms, simultaneous identification of multiple targets, high signal-to-noise ratio and low limits of detection.

<<6>> NANOPOROUS GOLD ELECTRODE ARRAYS FOR NUCLEIC ACID-BASED ELECTROCHEMICAL BIOSENSORS

Jovana Veselinovic[1], Suzan Almashtoub[1], Erkin Seker[2]

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[2]Department of Electrical & Computer Engineering, UC Davis, Davis, CA

Introduction: Molecular diagnostics have advanced the early detection of diseases, where electrochemical sensing of biomarkers (e.g., DNA, RNA, proteins) have shown considerable promise. Nanostructured electrodes generally enhance electrochemical sensor performance via several mechanisms, including increased number of capture probes per electrode volume and unique nano-scale transport phenomena. However, there is a lack of fundamental understanding when it comes to the electrochemical nano-scale sensing phenomena. The goal of this study is thus to provide insight into transport and electrochemical detection events occurring at nano-scale using nanoporous gold (np-Au) electrode as a model system for broadly-applicable design and optimization of nanostructure-enhanced biosensors, and test such an optimized device for multiplexed detection of breast cancer biomarkers.

Materials and Methods: Np-Au electrodes were fabricated by sputtering gold/silver alloy on glass slides as the precursor alloy. Fabricated samples were additionally processed to pattern the np-Au thin film into multiple electrode array (MAE) traces using UV laser ablation. Np-Au thin films were then dealloyed in nitric acid to produce unannealed np-Au morphology. Thermal annealing was used to generate annealed np-Au (Figure 1A). Planar gold (pl-Au) electrodes were fabricated in a similar fashion as the control smooth morphology. 26-mer single-stranded DNA (ss-DNA) capture probe was immobilized on the electrode surface via thiol chemistry. Square wave voltammetry (SWV) with methylene blue (MB) redox marker was used for DNA characterization. MB binds to ss-DNA via guanine (G) bases and serves as an indirect measure of amount of immobilized ss-DNA on the electrode. Upon target hybridization to the probe DNA, SWV signal decreases (denoted as percent signal suppression (% ss)), since G bases become less accessible to MB in the duplex configuration. Fluorescent dyes, OliGreen (ss-DNA) and PicoGreen (double stranded (ds-DNA)) were used to quantify detached (via electrochemical reduction of thiol-gold bond) or unbound DNA amount at the working electrodes.

Results and Discussion: The total charge transfer as a measure of immobilized probe DNA (obtained from baseline SWV curve) with respect to the OliGreen quantification of detached/unbound probe DNA show that while there is a linear increase in probe immobilization with increasing probe solution for pl-Au and annealed np-Au, a secondary trend emerges for unannealed np-Au (Figure 1B). It is plausible that DNA transport into the pores is hindered by "funnel-like" constrictions (cross section in Figure 1A); hence, a larger concentration gradient is necessary to sustain immobilizing the deeper pores of unannealed np-Au and more unbound probe accumulated for unannealed np-Au (data not shown). Unlike planar gold (pl-Au) electrodes, where % ss reaches a steady-state with increasing concentration of the grafting solution, the % ss displays peak performance at certain grafting solution concentrations followed by rapid deterioration and reversal of the % ss polarity, suggesting an unexpected case of increased charge transfer upon hybridization (Figure 1C). Fluorometric assessments of electrochemically-desorbed nucleic acids for different electrode morphologies reveal significant amount of DNA molecules (unhybridized and hybridized) remain within the nanopores post-hybridization (data not shown). To test the sensitivity and selectivity of the optimized sensor, three different multiple electrode arrays (MEAs) were used. The electrodes on each device were functionalized with distinct capture probes specific to a different breast cancer biomarker (BRCA1, BRCA2, p53) using electro-grafting by holding only one electrode at a positive potential at a time. The devices were then challenged with the different complementary DNA targets and interrogated via SWV. Significant signal suppression (~60%) was observed from the electrode that had the complementary probe sequence to the target in the sample, while the other two electrodes showed minimal change in signal indicating high detection selectivity (Figure 1D).

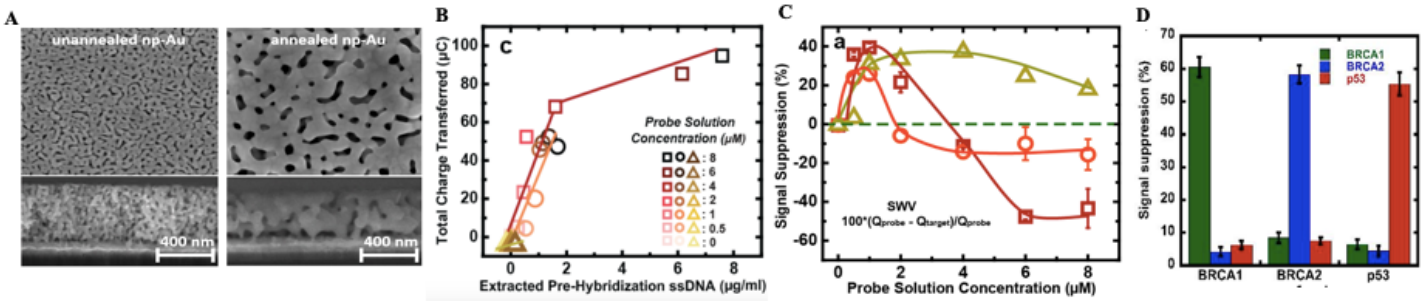

Figure 1. (A) Scanning electron micrographs of np-Au electrodes (top-view à top row; cross-sectional view à bottom row). (B) Effect of electrode morphology on the amount of immobilized DNA probe at varying probe solution concentrations, as quantified by both total charge transfer
(immobilized DNA) and OliGreen fluorescence (detached/unbound ss-DNA). (C) Post-hybridization %ss at varying probe solution concentrations.
(D) Multiplexed detection of breast cancer markers using MEA embedded in a microfluidic device.

Conclusions: We demonstrated that nanostructured electrochemical sensors exhibit anomalous sensing phenomena compared to smooth electrode-based sensors, particularly for samples with high DNA concentration. I addition, electrically guided DNA printing technique allows for detection of multiple biomarkers to ultimately improve diagnostic confidence.

<<7>> CHARACTERIZATION OF ELECTRIC FIELDS AT CANCER TISSUE AND CANCER CELL MIGRATION IN ELECTRIC FIELDS

Kan Zhu[1], Nicholas Hum[2], Brian Reid[1], Qin Sun[1], Gabriela Loots[2], and Min Zhao[1]

[1]Institute for Regenerative Cures, Departments of Dermatology and Ophthalmology, School of Medicine, University of California, Davis, CA 95616
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Background: Cancer growth interferes with local ionic environments, membrane potentials, and transepithelial potentials, resulting in small electrical activities in the tumor microenvironment. Electric fields have significant effects on cancer cell migrations (galvanotaxis/electrotaxis). We aimed to use unique probe systems to characterize electrical properties of cancer tissues, and migration of cancer cells in different organs in electric fields.

Methods: Cancer nodules from a murine breast cancer cell line (4T1-Red-FLuc-GFP) in immunodeficient mice (NSG) subcutaneously were dissected. Electric currents and potentials were measured using vibrating probe and glass microelectrode, respectively. 4T1-GFP cells isolated from different organs 4-6 weeks following tail vein injection were subjected to applied electric fields, and the electrotactic responses are quantified.

Results:
1) Cancer nodules produce electrical currents and showed heterogenous intratumor electric potentials. Four cardinal points surrounding each tumor were measured. Most of the measurements showed steady outward currents while some isolated points generated inward current. The magnitudes of the electric currents at tumor surface showed a strong correlation with tumor weights. We also used glass microelectrode to monitor the ITP at the same points of each tumor. It showed a similar pattern with the current measurements which supports the idea that the tumor electrical properties varied at different parts of the tumor due to the heterogeneity of the cancer tissue.

2) Cancer cells showed robust and stronger electrotaxis collectively than cells in isolation. We found that parental 4T1 cells and metastatic sublines in isolation showed random migration in electric fields, whereas, cells in monolayer response to electric fields and migrated to the anode.

3) Cancer cells metastasized to different organs showed different electrotaxis threshold and some subtle difference. The parental line and all metastatic sublines showed significant anodal migration in a field no less than 100 mV/mm ($p < 0.01$ compared with its no EF control), while 4T1 and its lung metastatic cell sheets could respond to an EF as low as 50 mV/mm ($p < 0.05$). Metastatic sublines isolated from lymph node showed significant weaker electrotaxis ($p < 0.05$ when exposed to 50 mV/mm or 100 mV/mm EF; $p < 0.01$ in 200 mV/mm EF). The directedness of the spleen-metastatic sheets was significantly lower when compare to the parental 4T1 cells in an EF of 100 mV/mm ($p < 0.01$). The lung-subline migrated significantly faster in isolation in the absence or presence of EFs, while the heart-subline migrated significantly faster in monolayer. Metastatic cells isolated form spleen showed lower migration speed in most of the conditions.

Conclusion: These results suggest that: 1) the tumor indeed generate an electric field at the tumor surface, and the tumor EFs could be enhanced during tumor growth; 2) the direction and magnitude of the electric currents at the tumor surface are inhomogeneous which may due to the heterogeneity of the tumor tissue, thus one or more electrical circuits may exist at the tumor surface; 3) EFs of physiological strength induced significant collective migration responses in the cancer cells. 4) Cancer metastatic sublines isolated from different organs may have subtle differences due to the differences in tumor microenvironments, including electric field, adhesion, and cell density.

<<8>> EPIGENETIC MECHANISMS UNDERLYING THE CARCINOGENIC EFFECTS OF CIRCADIAN CLOCK DISRUPTION

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Exposure to light at the wrong time of the day can have detrimental effects on our health, including increasing the risk of cancer. It has been shown in various studies that the elevated risk of cancer in shift workers is attributed to circadian clock disruption resulting from exposure to light at night. However, the mechanism by which circadian clock disruption results in increased cancer risk is unknown. We hypothesize that BRM, a SWI/SNF chromatin-remodeling complex that terminates transcription of circadian genes, establishes a dynamic chromatin landscape that generates rhythmic gene transcription in order to prevent transcription and replication machinery from colliding with one another. Because transcription and replication utilize the same template, they are likely to interfere with one another. This phenomenon is referred to as transcription replication conflicts (TRCs). When transcription and replication machinery collide, they generate torsional stress on the DNA that results in DNA damage and ultimately genome instability. Additionally, TRCs cause replication stress on the genome, which is a hallmark of precancerous cells. Here, we show that key clock proteins, CLOCK (CLK) and TIMELESS (TIM), regulate rhythmic BRM binding to the chromatin to establish a dynamic landscape, which may impose temporal separation on transcription and replication. Furthermore, because TIM stability is affected by light, we examined the effects of light on BRM occupancy and ultimately chromatin structure.

<<9>> IDENTIFYING NEW GENES INVOLVED IN TNBC THROUGH CRISPR ACTIVATION SCREENS

J Antionio Gomez, David J Segal, Colleen Sweeney

Breast cancer is the most commonly diagnosed cancer in the United States. Triple-negative breast cancer (TNBC) in particular, is well recognized for its aggressive biology, reflected in poor patient prognosis. Furthermore, TNBC disproportionately impacts young women and women of African and Hispanic heritage. TNBC patients are more likely to respond to chemotherapy than patients with other types of breast cancer BUT most TNBC patients do not achieve a complete pathological response (pCR), leaving them at a substantially (12-fold) elevated risk of death. Thus, identifying better methods to achieve a complete response and avoid drug-resistance has been of great interest. The focus of this study is to identify new genes involved in TNBC cell replication. In particular, our hypothesis is that the CRISPR-Cas family of proteins can be used to identify genes whose *activation* will suppress TNBC growth. Our approach has been to engineer new breast cancer cell lines with gene activation systems based on Cas9 nucleases that are catalytically inactive for DNase activity or "dead" (dCas9). These proteins will function as programmable DNA-binding platforms, to which transcriptional activating domains have been attached. We will present initial data on establishing stable cell lines through piggyback recombineering in MCF7 and HCC1937 cancer cells. These new isogenic cell lines express dCas9 tethered to transcriptional activation domains of VP64, HSF1, and P65 making it possible to activate genes when guide RNAs are transduced. Using these cell lines, we have conducted an unbiased genome-wide screen to identify genes whose activation leads to cell growth defects. A library of gRNAs targeting over 18,000 protein coding genes in humans was packaged into lentivirus and introduced into our newly engineered cell lines. To monitor the abundance of each gRNA, cells were collected at different time points post transduction and next-generation sequencing libraries were submitted for illumina sequencing. Our expectation is that gRNAs that recruit the activation machinery to genes involved in cell cycle replication arrest, apoptosis, or senescence will be depleted in the library. Conversely, we expect that genes whose expression provides a growth advantage will be enriched over time. These hits will be validated in a large panel of TNBC cell lines. The outlook of our work is to identify genes beyond "druggable-genome" that may be targeted through the new generation of genome and epigenome editing technologies.

Funding: NIH T32 in Oncogenic Signals and Chromosome Biology (J.A.G.)

This work was supported in part by gift funds from the UC Davis Comprehensive Cancer Center (D.J.S and C.S.)

<<10>> DUET: NOVEL SLIDE-SCANNING APPROACH FOR SPATIALLY MAPPING COLLAGEN DISTRIBUTION IN BREAST CANCER BIOPSIES

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Collagen is a major component of the extracellular matrix. Its presence specifically in the tumor microenvironment has been associated with various tumor cell behaviors, being implicated in cell adhesion, proliferation, and migration. Type, abundance and alignment of the collagen fibers in proximity to primary breast tumors, in particular, are emerging as a critical stromal feature, although connections between stromal phenotypes and cancer cell behavior are complex and not fully understood. For example, an initial step in cancer metastasis is migration of tumor cells through the extracellular matrix and into lymphatic or vascular systems; tumor cells seem to use collagen bundles as scaffolds along which such events occur. In addition, regions of dense collagen are co-localized with aggressive tumor cell phenotypes in numerous solid tumors, including breast, ovarian, pancreatic and brain cancers. However, sparse and well-aligned collagen fibers at the edges of tumors have also been reported to correlate with aggressive disease.

We report development and validation of a novel imaging methodology along with analysis tools that can extract collagen spatial distribution from conventional H&E slides, avoiding the need to employ additional stains or complicated and expensive optics. Our technique, termed DUET (Dual mode Emission Transmission microscopy), provides a simple means for highlighting collagen distribution patterns on existing standard histology slides; the extracted signals can then be subjected to downstream quantitative analytics. We have

performed a validation study on de-identified breast cancer specimens, to evaluate the validity and potential utility of the collagen images obtained with DUET technology, comparing them to standard collagen stains immunohistochemistry, picrosirius red and second harmonics generation microscopy.

We demonstrate the utility of this technology on existing specimens from 20 aggressive early-stage breast cancer patients that are known to be metastasis-free with at least 5 years of follow-up, along with stage-matched specimens from 20 patients who developed distant metastases in within 5 years after initial diagnosis. We show that DUET tumor-associated collagen patterns in these slides have promise as a breast-cancer prognostic biomarker, with applications in research and potentially in clinical settings.

<<11>> TARGETED IMAGING OF TUMOR ASSOCIATED MACROPHAGES

Junhan Zhou[1], Esther Chen[2], Wendy Liu[2], Angelique Y Louie[1, 3]

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Cancer remains a major health problem worldwide, and breast cancer is the most prevalent malignant disease of women[1]. In the tumor micro-environment, tumor associated macrophages (TAMs) represent a predominant component of the total tumor mass[2]. We propose that using SDIO (sulfated-dextran coated iron oxide nanoparticles) as an M2-macrophage-targeted. T2-based MRI contrast agent could be a promising approach to improve cancer diagnosis by facilitating monitoring of TAM activity. These agents will aid in understanding macrophage localization, phenotype variation within the tumor, and interaction with tumors. In this project, mouse models of breast cancer were imaged before, and 4h, 24h and 48h after IV injection with SDIO, and compared to untargeted DIO (dextran-coated iron oxide nanoparticles) as controls. TAMs uptake efficiency was determined from the signal intensity and T2* values of images. Different sulfation levels of SDIO (10:1 and 1:1 ratios of sulfur:iron), dosages of contrast agents, and tumor sizes were evaluated. Comparing the normalized mean signal intensity changes along time, mice with 25 mm^3 tumors injected with 15 mg/kg 10:1 SDIO and 30mg/kg 1:1 SDIO were 5.2 and 8.4 greater than the control DIO-injected group, while mice with 100 mm^3 tumors were 10.9 and 7.8 greater. Similar results were found for mean T2* values. In order to confirm that the nanoparticles accumulate in tumors, histological staining for activated-macrophage (F4/80) and iron (Prussian blue) were performed. We found that iron persisted in the SDIO-injected group through 48h-post injection, while no iron remained in the corresponding controls at 48h. Moreover, we found a species dependence in bone marrow uptake of SDIO. SDIO had higher accumulation in the Balb/c mouse bone marrow than in the bone marrow of C57Bl/6 mice. Since Balb/c mice are M2 macrophage dominant, while C57Bl/6 mice have high M1 macrophage responses in bone marrow derived immune system[3], these results suggest that SDIO may have higher uptake in M2 macrophage. Studies are underway to probe this further.

Acknowledgement
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Reference

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<<12>> INITIAL QUANTITATIVE EVALUATION OF ONCOLOGIC PATIENTS USING uEXPLORER 18F-FDG PET/CT SCANS

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^{18}F-FDG PET/CT is a cornerstone in staging and evaluation of response for many oncological diseases. However, current PET/CT scanners have limited field-of-view which could degrade image quality and limit the contrast resolution of the scanner. uEXPLORER PET/CT, recently installed and operational at UC Davis, is the world's first total-body scanner capable of simultaneously capturing tracer distribution over all the body organs in real-time.

In this retrospective image quality review, we aim to present initial quantitative evaluation of oncologic patients who have been scanned so far on uEXPLORER PET/CT.

Methods: uEXPLORER PET/CT images of 10 oncology subjects were used for this analysis (IRB waived, as anonymized images were considered non-human subjects). The images were acquired at 60-min after the intravenous injection of 5 mCi of ^{18}F-FDG (half the conventional activity) for a duration of 20 minutes; which were then sub-sampled into 5-, 10- and 15-min durations, each of them was reconstructed with and without point-spread function (PSF) modeling. Spherical volumes of interest (VOIs) were placed on ascending aorta or aortic arch to quantify SUVmean as a reference background tissue and coefficient of variations (COV) was calculated as (standard deviation/mean). Also, SUVmax and SUVpeak (mean SUV within 1-cm spherical ROI centered on maximum pixel of the lesion) for up to 5 target lesions were measured together with the ratio of SUVmax and SUVpeak to the BP SUVmean (rSUVmax and rSUVpeak, respectively).

Results: The lowest COV was seen for 15-min uEXPLORER scans (0.065±0.006) followed by those acquired for 20-min (0.067±0.015). Both were employing PSF modeling. COV calculated from 5- and 10-min were, respectively, 0.081 and 0.084 for PSF reconstructions, and 0.099 and 0.115 for reconstructions without PSF. The mean SUVmax, SUVpeak, rSUVmax for the largest target lesion were, respectively, 11.4±8.2, 8.0±6.6, 5.0±3.6, 3.5±2.8 for 10-min and 11.5±8.5, 7.8±6.2, 5.1±4.0, 3.5±2.8 for 20-min acquisitions.

Conclusions: This initial exploratory analysis showed that the background coefficient of variation (indicative of noise) shows minimal variability between different acquisition durations when employing half the usual injected dose of the radiopharmaceutical on uEXPLORER PET/CT. Furthermore, SUV metrics were stable for different reconstruction schemes.

Future analysis employing larger sample with clinical/histopathological correlation is being sought.

Acknowledgements: We thank Heather Hunt, Michael Rusnak, Mike Nguyen, Kristin McBride and Denise Caudle for their invaluable efforts in performing the scans.

<<13>> THE POTENTIAL BENEFITS OF USING THE EXPLORER TOTAL-BODY PET SCANNER FOR PAEDIATRIC IMAGING

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Objective: To demonstrate the potential benefits and reduction of risks to paediatric patients that may be achieved by using the EXPLORER Total-Body Positron Emission Tomography (PET) Scanner. A review of the current practices in paediatric PET scanning and the specifications of the EXPLORER scanner will be used. Rationale: PET scanners are widely used for paediatric oncologic imaging; from providing useful information when staging solid tumours, to monitoring the response to therapies, or assisting in the planning of radiotherapy treatment. However, PET scanners rely on the use of ionising radiation. Managing exposure to radiation is particularly important for paediatric patients due to two factors: depending on the age of the child

they are between two and ten times more sensitive to radiation than adults [1], and that children have a longer lifetime than adults during which cancer may develop from exposure to radiation after a latent period [1]. As exposure to radiation from medical imaging is a modifiable risk factor, steps should be taken to optimise imaging tests so that the lowest radiation dose is used.

Another potential issue is the use of general anaesthesia in paediatric patients. Movement during a PET scan results in decreased image quality, therefore paediatric patients may be sedated to limit this movement. However, the multiple use of anaesthesia in patients under the age of three has been associated with decreases in cognitive ability so ideally it would not need to be used [2].

Results: The EXPLORER Total-Body PET scanner is an improvement on the typical PET scanner in that it has a greatly increased geometric coverage that covers the whole body. The effect of this increased geometric coverage is an improvement in the sensitivity of the scanner by a factor of about forty for total-body imaging. Therefore, the EXPLORER scanner can be used for diagnostic scans with much lower injected activities or much faster imaging times, or a combination of the two.

A scan using the EXPLORER scanner of a small adult (117 lbs) using an injected activity of 1/20th (0.62 mCi) of the normal dose has been shown to have diagnostic image quality, as seen in figure 1. This study further presents a quantitative assessment of image quality obtained from seven very low dose (mean injected activity of 0.57 mCi) healthy volunteers scanned on EXPLORER where the coefficient of variation of the standard uptake value of the liver is 0.1. Therefore setting precedent that large dose reductions are possible for paediatric patients scanned on the EXPLORER scanner.

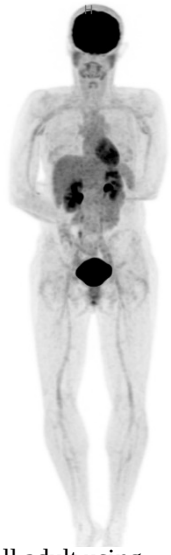

Figure 1. EXPLORER scan of small adult using reduced dose.

Conclusions: Using the EXPLORER scanner compared to a typical PET scanner could result in both lower doses to the patient, reducing the lifetime risk of developing cancer which is especially important in paediatric patients, and lower scan times, potentially removing the need for the use of general anaesthetic and its associated risks.

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<<14>> EXPLORING THE POTENTIAL OF uEXPLORER FOR HALF-MILLISIEVERT PET/CT IMAGING

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Use of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography integrated with computed tomography (PET/CT) has transformed tumor staging and treatment response evaluation in a wide variety of pediatric cancers. Despite its great potential and success in the past, broader use of PET/CT in pediatric patients has been restricted because of concerns that the associated radiation dose [7 millisievert (mSv) per PET scan and 1-2 mSV per low-dose CT scan] may result in increased risk for secondary cancer. Much effort has been devoted to lower radiation dose in imaging, e.g., through the Image Gently campaign. Our goal is to reduce the total radiation dose of PET/CT to only about half mSv with 0.35 mSv from FDG-PET and 0.1-0.2 mSv from CT. In this poster, we first demonstrate using patient scans that the new high-sensitivity total-body uEXPLORER PET scanner has the great potential to reduce FDG dose by a factor of 20 (or more) with equivalent or better image quality when compared to conventional PET scanners. The reduction of injected FDG dose can reduce

the effective dose of FDG-PET imaging from 7 mSv to 0.35 mSv. After the PET dose reduction, the effective dose of x-ray CT will then become dominant (1-2 mSv) in the overall radiation dose of PET/CT imaging. Hence, the poster also describes our ongoing developments of new data processing and reconstruction approaches to further reduce the CT dose. Our approaches explore both available PET data and x-ray CT data from a PET/CT scan to improve ultralow-dose CT image reconstruction. The ultimate goal is to reduce the CT dose by a factor of 10 to approximately 0.1-0.2 mSv with maintained image quality, thus enabling half-mSv PET/CT imaging. The significant reduction of radiation exposure will allow PET/CT to be used more widely and safely in pediatric patients so that they can benefit greatly from functional PET/CT imaging without potential compromise on their life quality after survival from cancer.
Acknowledgements: This work is supported in part by a UCD CCC Pediatric Oncology Pilot Grant.

<<15>> DEVELOPING A NOVEL DOSIMETRY FOR LIVER CANCER RADIOEMBOLIZATION USING HEPATIC ARTERY BLOOD FLOW SIMULATION

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Radioembolization with yttrium 90 (^{90}Y) microspheres is a method that has been increasingly used for liver cancer treatment. In this method, the radioactive microspheres are injected into the hepatic artery to be transported to the tumor and internally irradiate it. An accurate pretreatment dosimetry is crucial to ensure the delivery of a sufficient dose to the tumor while limiting the dose to the healthy liver. However, available methods are unable to estimate the dose accurately and precisely due to simplistic assumptions. For example, they assume that the ^{90}Y microspheres are homogeneously distributed inside the hepatic lobes, which is inaccurate. To address this problem, we are developing a new dosimetry which is based on computational fluid dynamics (CFD) simulation of blood flow in the hepatic arterial tree. Figure 1 shows the main three steps of the proposed method. The hepatic arterial tree of the cancer patient is first segmented from the standard-of-care cone beam CT (CBCT) scans using a fast marching method algorithm. The blood flow is then computed for each patient by solving Navier-Stokes equations of mass and momentum conservation. Microsphere trajectory to the arterial outlets, including tumor, is estimated from the blood flow streamlines. Considering the microsphere density and blood viscosity, it can be assumed that the microspheres closely follow these streamlines. The dose to the tumor and surrounding parenchyma is finally calculated from the number of microspheres delivered to each outlet and using a dose point kernel method to model the physics of the beta emitter ^{90}Y (maximum energy 2.28 MeV). We also compare our simulation results with the ^{90}Y activity distribution imaged using positron emission tomography (PET). Our results show the potential of this method to improve the dosimetry of liver cancer radioembolization. Further results will be presented in our poster.

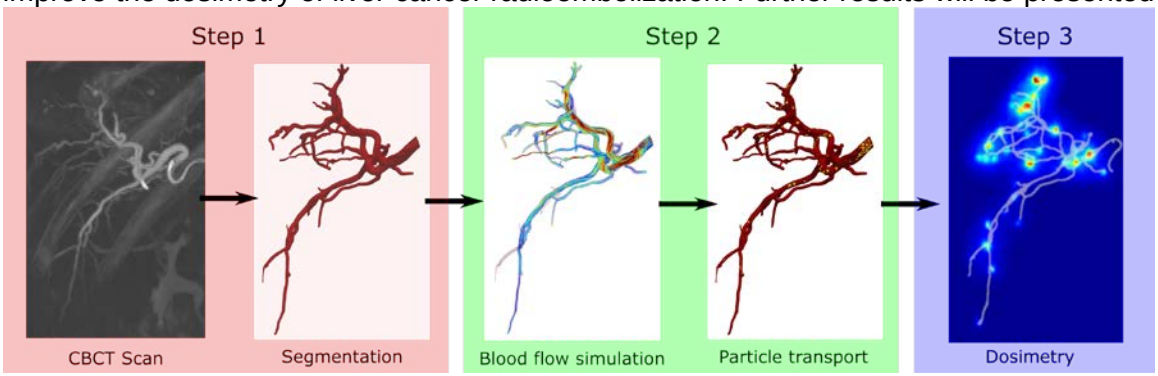

Figure 1. Main three steps of the proposed dosimetry method. From left to right, (red box) hepatic arterial tree segmentation from CBCT scans, (green box) CFD simulation of blood flow inside the segmented hepatic arterial tree from the previous step, (blue box) dosimetry estimation using the number of microspheres delivered to each outlet.

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<<16>> QUANTIFYING DRUG DELIVERY TO SINGLE TUMOR CELLS IN A 3D *IN VITRO* MODEL OF THE TUMOR MICROENVIRONMENT

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Purpose: Cell-to-cell variability is a defining feature of cancer, yet much remains unknown about how this variability contributes to drug resistance. Understanding tumor heterogeneity at the single cell level and identifying dormant or cancer stem cells that are drug resistant is critical in developing effective therapies for cancer. To date, little is known regarding single cancer cell drug exposure or uptake. Fluorescent optical reporters used to label proteins and biomolecules has greatly advanced our understanding of cancer biology, but coupling optical probes to small molecule pharmaceuticals significantly alters their structure and can affect their function and metabolism. Thus, direct quantification of single cell drug uptake using fluorescent labels remains problematic. On the other hand, radiolabeling pharmaceuticals generates chemically identical analogs. Therefore, we seek to use isotype labeling as a method to quantify single cell heterogeneity of drug uptake.

Methods: Lawrence Livermore National Labs (LLNL) has developed a biological Accelerator Mass Spectrometer (AMS) that quantifies rare isotopes of carbon such as 14C. Drugs containing carbon can be 14C radiolabeled with insignificant changes to the structure and function. The AMS moving wire sample interface has been optimized to measure small liquid samples and quantify radiolabeled carbon at zeptomole levels, which is sensitive enough to quantitate the amount of drug uptake expected at the single cell level. To achieve single cell AMS measurements, we developed a single cell isolation and manipulation platform and integrated it with the existing moving wire interface. Cells were visually verified and counted prior to AMS measurement to generate the first AMS measurements of single biological cells. Using cells stably labeled at different levels of 14C we verified normalized bulk measurements align with single cell 14C measurements. Next, carboplatin, a first line chemotherapeutic, was exposed to MDA-MB-231 breast cancer cells at varying concentrations to determine IC50. We followed up with radiolabeling carboplatin and exposing MDA-231 cells at the IC50 concentration for 4, 24, and 48 hours. After exposure period, cells were collected, counted, and analyzed both at the single cell level and in bulk for 14C content, a measure of carboplatin uptake.

Results: IC50 concentration of carboplatin to MDA-MB-231 cells for 48 hours was 358 uM. Cells treated for 24 hours had the highest concentration of drug (0.16 amol 14C per cell). The lower value at 48 hours may be a due to death of cells with higher drug uptake, leaving alive cells with lower drug uptake to be analyzed by the AMS. Comparing single cell population data to bulk averages for carboplatin uptake per cell, both the 4 and 24 hour time points single cell population means did not differ from the estimated carboplatin uptake per cell determined by bulk measurements. The mean estimate of cell uptake at 48 hours from averaging single cell measurements was lower than the estimated uptake from bulk samples.

Conclusions: AMS technology provides direct quantification of 14C radiolabeled drug uptake at the single cell level. This information will enhance our understanding of cancer cell heterogeneity in drug uptake and thus mechanisms of drug resistance.

This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

<<17>> OPTICS-BASED SENSORS FOR MAGNETIC *NANO*-BEAD DETECTION AND CANCER TISSUE IMAGING WITH MAGNETIC SIGNATURE AS CONTRASTS

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Cancer is addicted to iron. There is increasing evidence that cancer is associated with dysregulation of cellular iron metabolism, resulting in accumulation of iron in cancer cells, particularly cancer stem cells. In the last few years, iron- and reactive oxygen species dependent cell death or ferroptosis has attracted attention as an emerging strategy for cancer therapy. A sensor that can detect iron metabolism in real time in live cancer cells,

cancer organoids and *in vivo* tumor will be invaluable for cancer biology research. As cancer initiating cells or cancer stem cells are known to have higher iron storage, a sensitive and specific sensor for magnetic properties of iron may allow researchers to reliably identify and sort these cells in a label-free manner.

Commercially available magnetic microscopic sensors based on magneto-optical effects have inadequate sensitivities to weak magnetic signatures such as those of individual magnetic *nano*-beads often used as either carriers or tags of biomolecular or cellular samples. Superconductor Quantum Interference Device (SQUID) sensors have superior sensitivities. Yet they require expensive and cumbersome cryogenic coolant to operate and have very poor spatial resolution. To detect single *nano*-magnetic beads and image tissues based on intrinsic as well as extrinsic magnetic contrasts, there are needs for room-temperature optics-based sensors having orders of magnitude better sensitivities than current devices and being readily configured into microscope. Sagnac Interferometric sensors can meet such needs. Such a sensor will enable us to monitor endogenous magnetic signals inside living cells, tumor organoid culture, tumor tissue sections, and perhaps even *in vivo*.

We developed a prototype Sagnac interferometry-based magnetic sensor with the capability of detecting magneto-optic Kerr rotations as small as 3×10^{-7} radians/$\sqrt{\text{Hz}}$, thus 2 ~ 3 orders of magnitude better than commercially available instruments. For a set of preliminary data on Sagnac interferometric microscopy of magnetic nanobeads, we built a normal-incidence scanning Sagnac interferometer and with it acquired images of 200-nm magnetic beads immobilized on a glass slide surface. These beads are donated by Nvigen. The 200-nm beads are polarized with an external magnetic field of 130 Oe along the surface normal. The scanning Sagnac sensor reads the Kerr rotation due to the magnetization perpendicular to the surface (a.k.a. the polar Kerr rotation). Using these images as the preliminary results, we have submitted an NIH/NCI R21 grant application that is currently under review.

To make the Sagnac interferometric microscopy capable of imaging tissues *without* externally applied magnetic field, we explored an oblique-incidence scanning Sagnac microscope configuration. The new geometry enables us to image magnetic beads using three magnetic contrasts: polar Kerr rotation, transvers Kerr rotation, and longitudinal Kerr rotation. Each corresponds to one of the three Cartesian components of the magnetization associated with the bead.

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<<18>> NANO-SN-38/VINCRISTINE AGAINST PEDIATRIC CANCERS

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Nanoparticle-based theranostic agents have emerged as a new paradigm in nanomedicine field for integration of multimodal imaging and therapeutic functions within a single platform. However, the clinical translation of these agents is severely limited by the complexity of fabrication, long-term toxicity of the materials, and unfavorable biodistributions. We have recently reported a “One-Pot” fabrication of highly versatile and biocompatible poly(vinyl alcohol)-porphyrin-based nanotheranostic agent. Our novel highly versatile and biocompatible theranostic poly(vinyl alcohol)-porphyrin nanoparticles (PPNs) is extremely simple and robust. Through a “one-pot” fabrication including the chelation of metal ions and encapsulation of hydrophobic drugs during the nanoparticle formation by the surpramolecular assembly of a very simple and biocompatible building block [poly(vinyl alcohol)-porphyrin conjugate], we could conveniently produce multifunctional PPNs that integrate optical imaging, positron emission tomography (PET), photodynamic therapy (PDT), photothermal therapy (PTT) and drug delivery functions in one formulation. Doxorubicin can be loaded efficiently through non-covalent encapsulation by PPNs. Upon illumination by near infrared light at a single excitation wavelength, PPNs could be activated to release reactive oxygen species, heat and drugs simultaneously at the tumor sites in mice bearing tumor xenograft, resulting in complete eradication of tumors.

We have recently exploited the reversible boronate-catechol bond to covalently load therapeutic payloads onto the PVA polymer backbone of our PPN platform, and successfully loaded SN-38 into PPN. We are currently developing methods to do the same for vincristine. In addition, we plan to use similar strategy to load anti-sense peptide nucleotide for therapeutic applications against pediatric cancers with overexpression of unique oncogenic driver genes.

Acknowledgments: This work was funded by the UC Davis Comprehensive Cancer Center CCSG Pilot Fund.

<<19>> THERMO-RESPONSIVE pNIPAM NANOPARTICLES AS A NEW STRATEGY TO DELIVER THE CHEMOTHERAPEUTIC AGENT PIPLARTINE AND ANTI-INFLAMMATORY PEPTIDE YARA IN THE MAMMARY GLAND FOR LOW-GRADE DCIS TREATMENT

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Introduction: The high incidence of breast tumors and the lack of strategies for local management of non-invasive, low grade ductal carcinoma *in situ* (DCIS) and atypical lesions led us to propose the development of nanocarriers for intraductal drug administration. Aiming to obtain a prolonged drug retention and localization at the target site, improved efficacy and reduction of systemic adverse effects, we synthesized a thermoresponsive poly(N-isopropyl acrylamide, pPNIPAM) nanoparticle (NP) to encapsulate the chemotherapeutic agent piplartine. pPNIPAM thermoresponsive NPs are water-soluble at temperatures below their lower critical solution temperature (LCST) and undergo hydrophobic collapse at physiological conditions, allowing controlled drug release. Piplartine is an alkaloid / amide component of *Piper* species and shows significant cytotoxic and antiproliferative activity in cancer cells. Piplartine was co-encapsulated with the peptide YARA, an inhibitor of MAPKAP Kinase 2 (MAPK2), to improve the nanocarrier antitumor effect.

Methods: Non-crosslinked NIPAm was polymerized forming the core of the NP core-shell complex. Acrylic acid (AAc), NIPAm and 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) were polymerized around the core with degradable cross-linker N,N′-bis (acryloyl)cystamine (BAC). NPs were dialyzed for 2 weeks against milliQ water in 10 kDa dialysis tubing generating hollow NPs (hNP). hNPs diameter and zeta potential were determined using dynamic light scattering (DLS) and electrophoretic light scattering (ELS), respectively. Drug loading into the lyophilized hNPs was performed at 4°C for 24 h by swelling in the presence of peptide YARA and piplartine. To characterize drug release, loaded hNPs were suspended in 1x PBS at 37°C and aliquots were collected at predetermined intervals up to 120 h. hNPs were pelleted via centrifugation and the supernatant was collected for chromatography analysis. The influence of nanoencapsulation and association of drugs on formulation cytotoxicity against breast cancer (T47-D and MCF-7) cells was assessed using MTS Tetrazolium Assay after 72 h treatment with unloaded hNP, hNP containing piplartine (hNP-PIP) and hNP containing piplartine and YARA (hNP-PIP-YARA) and compared with piplartine in solution (in DMSO) as a control. To evaluate whether IC50 reduction was mediated by a more efficient drug delivery, cellular uptake was assessed after cell incubation with nanoparticles loaded with rhodamine (hNP-RHO) or rhodamine solution; non-treated cells were used as a control. After 72 h incubation, cells were rinsed with PBS and fixed with 4% paraformaldehyde for 30 min. Nuclei was stained with DAPI, and confocal microscopy was used for cell analysis.

Results: The hydrodynamic diameter and zeta potential of unloaded hNPs were 344.9 ± 63.2 nm (polydispersity index of 0.075 ± 0.01) and -31.3 ± 8.0 mV, and drug encapsulation did not affect these parameters. Hollow hNPs encapsulated 0.80 ± 0.05 mg piplartine/mg hNPs and 0.55 ± 0.10 mg YARA/mg hNPs. Diameter decreased 55 ± 8.6% in temperature sweep from 17°C to 42°C, demonstrating the effect of rising the temperature above the LCST. Piplartine release from the hNPs within the first 2 h was 17% ± 5.4 while YARA exhibited a high initial burst release (27% ± 4.6); after 120 h, the piplartine and YARA total release were 45% ± 6.3 and 69.8% ± 7.2, respectively. Cell viability was approximately 99% after 72 h of treatment with unloaded hNP at 200 µg/mL, suggesting that they did not exhibit cytotoxicity. Piplartine concentration required to reduce cell viability to 50% (IC50) when used as a DMSO solution was 10.6 µM in MCF-7 and 9.5 µM in T47-D. Piplartine encapsulation (NP-PIP) decreased IC50 by 1.6 (6.6 µM) and 1.5 (6.4 µM) times in

MCF-7 and T47-D respectively. Further IC50 lowering of 2.2 times (4.7 μM) in MCF-7 and 3.2 times (2.9 μM) in T47-D were observed due to the piplartine combination with YARA (hNP-PIP-YARA). Cell treatment with rhodamine solution resulted in a lower fluorescent, while treatment with hNP-RHO resulted in a strong and homogeneous fluorescence staining within the cells, demonstrating hNP ability to promote cell penetration.

Conclusion: These results demonstrate the ability of pNIPAM nanoparticles to co-encapsulate piplartine and YARA, and reduce piplatine IC50 in breast cancer cell lines. This effect seems to be associated with a more efficient drug delivery mediated by the nanoparticles, as suggested in cells treated with rhodamine-loaded nanoparticles in comparison with a solution of the fluorescent marker. These results suggest the potential use of pNIPAM nanoparticles for localized DCIS and atypical lesions treatment.

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<<20>> GENERATION OF NANO-THERAPEUTIC APPROACHES FOR ONCOGENIC HERPESVIRUS MEDIATED CANCERS

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Primary effusion lymphoma (PEL) is a very aggressive form of Non-Hodgkin's lymphoma caused by Kaposi's sarcoma-associated herpesvirus infection. Current chemotherapeutic approaches result in dismal outcomes and need significant improvements. We have been establishing on-demand drug releasing and targeting nano-theranostics (OTNs) for the delivery of synergistic molecular medicine to increase the efficacy and minimize the toxicity of the treatment.

In this study, we first searched a drug combination suitable for PEL treatment. We reasoned that an ideal drug combination would be to robustly induce KSHV reactivation from latently infected cells to expose neo-antigens and kill resident cancer cells without allowing completion of viral replication. In this end, we found that the combination of bortezomib (BTZ) with BET-inhibitor, OTX-015, synergistically increased viral gene expression from KSHV-latently infected cells, while it inhibited production of capsidated viral DNA in supernatant. Importantly, supplementation of OTX-015 also inhibited secretion of IL-10 from BCBL-1, which results in modulation of tumor microenvironments. We found that OTX-015 strongly inhibited M2 macrophages polarization in vitro in the presence of BCBL-1 culture media and also in a xenograft mouse model. BTZ and OTX-015 could be efficiently loaded into our disulfide crosslinked nanoparticles at very high loading efficiency with a relatively small size. Encapsulating the drug combination into nano-carrier increased the maximal tolerate dose for 3-folds, and further inhibited both IL-10 and IL-6 expression in tumors. Taken together, our studies set a stage to further evaluate the nano-formulated drug combination in animal models.

<<21>> GENOMIC LOOPING FORMATION BETWEEN KSHV LATENT CHROMOSOMES AND HOST CHROMOSOMES; IDENTIFICATION OF PREFERENTIAL DOCKING SITES FOR LATENCY ESTABLISHMENT

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We previously showed that KSHV episomes form both inducible and pre-wired genomic loops, and that active transcription is important for inducible genomic looping and its distal gene activation. In this study, we utilized Hi-C analysis to examine genomic looping formation between KSHV episomes and host chromosomes in naturally infected primary effusion lymphoma cells. Additional enrichment steps incorporated into our Hi-C protocol increased the number of valid di-tags by 1,000-fold. This allowed us to prepare high-resolution KSHV 3D-genomic maps at 500 bp resolution, and also identify preferred interaction sites of KSHV episomes on host cell chromosomes.

Within KSHV epsiomes, KSHV forms several clear topology associated domains (TADs). Triggering reactivation significantly reduced genomic loops within each TAD, but increased genomic interactions outside of the TAD domains. This indicated that reactivation triggered a shift in KSHV episome conformation from a "closed" to "open" conformation, which allows each TAD to interact more freely with other domains. Single-primer PCR-based 3C studies indicated that these inducible genomic loops were primarily occurred in *cis*.

For interactions with host chromosomes, we found several highly enriched genomic loci on human chromosomes 2, 7, and 8, while KSHV episomes were largely excluded from sex chromosomes. KSHV episome interaction sites were most frequently seen near the H3K27 acetylation marks, possibly targeting genomic enhancer regions. The genomic looping formation with host chromosomes was significantly reduced when reactivation was triggered, with the exception of a few genomic loci. Consistent with global translocation of cellular RNA pol II to the viral episomes during reactivation, genomic loops within host TAD domains were globally reduced; this is similar to the phenotype observed during the entrance into cellular quiescence. By closely residing cellular enhancer regions, viral genomes may synchronize their own gene expression program with specific cellular pathways and/or place the enhancer under control of the virus.

<<22>> MAREK'S DISEASE VIRUS CAPTURE Hi-C WITH CHICKEN LYMPHOMAS REVEALED MULTIPLE INTEGRATED MDV GENOMES WITH POSSIBILITIES OF VERTICAL INFECTIONS

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Several herpesviruses including human herpesvirus 6A/B and Marek's disease virus (MDV) encode telomere like sequences in their genomes that facilitate integration of the viral genome into telomeres, the terminal repeat regions of host chromosomes. We hypothesized that integration of the viral genome into host chromosomes may alter the host genomic structure and function that are associated with highly-oncogenic phenotype of MDV. To reveal genomic interactions between MDV genomes and host chromosomes in chicken T-cell lymphomas, we have performed Capture Hi-C studies with an additional enrichment step utilizing custom-made MDV tiling oligos prior to deep-sequencing. Genomic looping formation within MDV genomes as well as with host chromosomes were mapped and visualized.
Within MDV genomes, our results clearly revealed two topology associated domains (TADs) that encompassing either unique long (UL) or unique short (US) region, indicating two unique regions are insulated and independently regulated. Each MDV TAD also contains transcriptionally active sites that are located in adjacent repeat regions (TRL/IRL and IRs/TRs). Two repeat regions (TRL/IRL and IRS/TRS) form genomic loops more frequently than others, showing these active regions are physically neighboring each other in 3D. Interestingly, the MDV capture-Hi-C also identified sites of MDV integration within chicken chromosomes. Surprisingly, freshly isolated chicken T-cell lymphomas from a chicken and a previously established chicken T-cell line (MSB1) showed several identical MDV integration sites in chicken chromosomes, suggesting the presence of inherited transfer mechanisms similar to HHV6A/B, and several MDV genomes may be integrated during evolution. However, this also raises a concern for poultry industry regarding use of live vaccines for MDV; inocula that may become an endogenous virus following vaccination and the potential for subsequent germ-line transmission. Further studies will be needed for risk assessment of the inherited viral genomes.

<<23>> EXPLOITING LYSOSOME-MEDIATED CELL DEATH IN CANCER THERAPY

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Cancer stem cells (CSCs) are a rare, chemotherapy-resistant population of tumor cells that are uniquely capable of initiating tumor growth, metastasis, and recurrence. We examine the notion that hexamethylene amiloride (HMA), a derivative of the FDA-approved potassium sparing diuretic amiloride, holds promise as a novel anti-CSC therapeutic. Our recent studies indicate that HMA engages a novel lysosome-mediated programmed necrotic cell death pathway to specifically kill breast cancer cells regardless of their molecular

profile, proliferative status, or species of origin. Further, HMA is potently cytotoxic toward isolated CSC populations from breast and other tumor types, whereas conventional chemotherapies kill only rapidly dividing bulk tumor cells and problematically induce normal tissue damage. Nonetheless, HMA's mechanism of cancer cell cytotoxicity has yet to be elucidated. We hypothesize that HMA triggers lysosomal membrane permeablization (LMP) and cathepsin protease release to ablate heterogeneous tumor cell subsets including CSCs. Our preliminary studies suggest HMA destabilizes lysosomal membranes by altering membrane lipid dynamics, leading to lysosome rupture. This work will expose a key vulnerability intrinsic to cancer cells that could be targeted with HMA or with the future development of alternative agents.

We thank Jonathan Van Dyke for technical assistance with fluorescent activated cell sorting and Qian Chen for histology consultation.

<<24>> WNT/PLANAR CELL POLARITY SIGNALING PROMOTES BREAST CARCINOMA CELL COLLECTIVE MIGRATION AND INVASION

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Our understanding of the cellular mechanisms governing carcinoma invasiveness and metastasis has evolved dramatically over the last several years. The previous emphasis on the epithelial-mesenchymal transition as a driver of the migratory properties of single cells has expanded with the observation that carcinoma cells often invade and migrate collectively as adherent groups. Moreover, recent analyses suggest that circulating tumor cells within the vasculature often exist as multicellular clusters, and that clusters more efficiently seed metastatic lesions than single circulating tumor cells. While these observations point to a key role for collective cell migration in carcinoma metastasis, the molecular mechanisms driving collective tumor cell migration remain to be discerned. Wnt/planar cell polarity (Wnt/PCP) signaling, one of the non-canonical Wnt signaling pathways, mediates collective migratory events such as convergent extension during developmental processes and Wnt/PCP components are frequently dysregulated in solid tumors. We demonstrate that aberrant activation of Wnt/PCP signaling promotes collective cell migration and invasion in breast cancer. We show that the non-canonical Wnt ligand Wnt5a potently simulates the collective migration and invasion of tumor cells mediated by Keratin14-positive cells at the tips of invading multicellular strands in *ex vivo* organoid assays. Visualization of Wnt/PCP components and active RhoA GTPase at the leading edge of actively migrating breast cancer cells suggest a model where Wnt/PCP signaling component localization to the leading edge of migrating breast cancer cells regulates the spatio-temporal activity of actin cytoskeletal effectors to govern protrusive membrane activity that drives cellular migration.

<<25>> WNT/PLANAR CELL POLARITY SIGNALING CONTRIBUTES TO GLIOBLASTOMA MULTIFORME INVASIVENESS

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Glioblastoma multiforme (GBM) is the most common form of malignant brain cancer, and is highly aggressive, recurrent, and difficult to treat. The highly infiltrative nature of GBM cells diminishes the clinical efficacy of surgery, and while the prospect of more effective patient-tailored therapies has been explored, such strategies have thus far failed because these tumors are inherently highly resistant. Wnt/Planar Cell Polarity (Wnt/PCP) is a non-canonical Wnt signaling pathway that interprets global directional cues to produce locally polarized cell behavior, leading to increased cell motility and invasiveness. Wnt/PCP is critical for embryonic developmental processes, where it modulates cell adhesion and migration. The emerging role for Wnt/PCP signaling in tumor malignancy underscores the recurring theme that tumors reactivate developmental programs to promote their aggressive behaviors. Expression patterns of Wnt/PCP pathway components strongly suggest that GBM tumors

engage the pathway to promote invasiveness and therapeutic resistance, underscoring the notion that a deeper understanding of Wnt/PCP in GBM could uncover novel therapeutic approaches. Our studies point to necessary roles for pathway components Wnt5a, Fzd7 and Vangl1 in GBM motility and invasiveness, and suggest a model whereby Wnt/PCP signals through Rho family GTPases to direct the formation of filamentous actin-rich protrusions at the leading edge of migratory GBM cells. Collectively, our observations highlight the importance of Wnt/PCP in promoting GBM malignancy, and suggest that interference with pathway signaling may offer an avenue toward the development of novel and more effective GBM therapeutic strategies and agents.

<<26>> USING ADVANCED MASS SPECTROMETRY TECHNIQUES TO EXPLORE NOVEL METABOLIC DIFFERENCES IN VARYING GRADES OF MENINGIOMAS

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Rationale: As more information emerges on metabolic changes in the brain from genetic mutations and disease, mass spectrometry methodologies are needed to investigate cellular changes in diseased tissue further. Many techniques are using old technologies that lack sensitivity and selectivity, which hinders the discovery of new features. By utilizing targeted and untargeted metabolomics workflow, which can be integrated with other omics using a single sample, we can annotate a large number of metabolites with known structure and provide greater insight on metabolic changes.

Methods: Fresh frozen tissue from 12 patients (57% women, 43% men; mean age: 48) who underwent surgical resection or biopsy for newly diagnosed brain masses. Two patients had matched, normal, healthy, dura matter resected that allowed for case/control analysis within one patient. Of the 12 samples analyzed, 58% were Grade 1 Meningiomas and 42% were Grade 2 Meningiomas.

We collected 10 mg of tissue and extracted for GC-TOF (primary metabolism), RPLC-QTOF ESI(±) (lipidomics) and HILIC-HRMS ESI(±) (biogenic amines) analysis. Data was processed using MS-DIAL, and in-silico structure predictions were made using MS-FINDER. Statistical analysis was performed using R.

We adopted our method to allow isolation of RNA on individual samples, providing a multi-omic methodology for an increased sample phenotyping.

Results: Our novel methods allow us to use isotope standards and MS2 quantification of key disease metabolites in addition to untargeted analysis for both metabolomics and lipidomics. These methods allow us to provide quantification for knowns with the ability to also measure unknown features. Primary metabolism and lipidomics showed significant differences between Grade 1 and Grade 2 tumors.

Over one thousand total metabolites were identified and annotated. Metabolites were grouped into one of fifteen classes based on chemical ontology and function. The classes were as follows- total amino acids (AA), basic AA, cyclic AA, sulfur-containing AA, branched-chain AA, dipeptides, histidine-containing dipeptides, vitamins and cofactors, glutathione metabolites, acylcarnitine's, sphingomyelins, phosphatidylethanolamines, phosphatidylinositol's, cardiolipins, and nucleic acids.

Conclusions: Using our combined targeted and untargeted metabolomics methods, we found multiple classes of metabolites that were enriched in Grade II tumors compared to Grade I tumors, pointing towards possible pathways that drive malignancy.

<<27>> TARGETING MITOCHONDRIAL METABOLISM FOR SELECTIVE DEATH OF GLIOBLASTOMA STEM-LIKE CELLS

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Glioblastoma Multiforme (GBM) is arguably the most aggressive, malignant primary brain tumor in adults with a very poor prognosis. GBM is the most prevalent form of brain tumor (55% of all cases) that contains self-renewing and tumorigenic cancer stem-like cells known as glioma stem-like cells(GSCs) that drive chemoresistance and lethality. As the more tumorigenic, stem-like cells had less mitochondrial activity, we examined whether these cells may be sensitive to classical mitochondrial inhibitors. The classic mitochondrial-specific inhibitors oligomycin A, antimycin A, and rotenone killed glioma stem cells higher than the differentiated glioma cells. Because classical mitochondrial inhibitors are likely to elicit troublesome toxicity in human patients, we tested 3 safe FDA-approved drugs--trifluoperazine, mitoxantrone, and pyrivinium pamoate that are also mitochondrial inhibitors. In contrast to the SoC GBM therapeutic temozolomide, which did not trigger cytotoxicity in glioma stem cells even at 100 μM concentration, trifluoperazine, mitoxantrone, and pyrivinium pamoate revealed higher cytotoxicity in glioma stem cells about 30-50 fold more effectively. Thus, we hereby demonstrate that GSCs can be specifically and preferentially targeted by both classical and FDA-approved mitochondrial inhibitors, which are about 40-fold more cytotoxic than the SoC temozolomide. Overall, our study demonstrates that targeting mitochondrial function could present a potential therapeutic option for GBM treatment.

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<<28>> MITOCHONDRIAL HETEROGENEITY IN PATIENT-DERIVED GLIOBLASTOMA STEM-LIKE CELLS

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Glioblastoma Multiforme (GBM) continues to be one of the most incurable cancers due to a high incidence of tumor recurrence and resistance to Temozolomide (TMZ), the standard of care (SoC) for GBM chemotherapy. GBMs contain a small population of glioma *stem-like cells (GSCs)* which drive resistance and lethality. We examined mitochondrial metabolic differences in patient-derived glioma cells. Overall, more tumorigenic and invasive GSCs showed less mitochondrial activity than less tumorigenic GSCs. More tumorigenic cells had significantly lower mitochondrial content as measured by the mitochondrial copy number. Correspondingly significantly lower expressions of mitochondrial DNA encoded genes such as the ND2 subunit of mitochondrial complex I and cytochrome B were also observed in the more tumorigenic GSCs. Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or Nrf2) is one of the major antioxidant defense pathways associated with mitochondrial biogenesis/activities. We hereby demonstrate that the more tumorigenic GSCs show significantly lower Nrf2 activity as measured by the Heme oxygenase 1 (HO-1) expression at the RNA level. The HO-1 expression at the RNA level can be a potential biomarker for the tumorigenicity and invasiveness. Thus, we hereby demonstrate that more tumorigenic GSCs contain lower mitochondrial number and activity than the highly tumorigenic GSCs. Overall, our study demonstrates patient-derived GSCs show mitochondrial heterogeneity which can be a potential therapeutic target for GBM.

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<<29>> RAD51: A PROMISING AND NOVEL TARGET FOR ANTICANCER THERAPY

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Introduction: The *RAD51* gene provides instructions for making a protein that is essential for repairing damaged DNA. Breaks in DNA can be caused by natural and medical radiation or other environmental exposures and can also occur when chromosomes exchange genetic material in preparation for cell division. The RAD51 protein binds to the DNA at the site of a break and encases it in a protein sheath, which is an essential first step in the repair process. In the nucleus of many types of normal cells, the RAD51 protein interacts with many other proteins, including BRCA1 and BRCA2, to fix damaged DNA. The BRCA2 protein regulates the activity of the RAD51 protein by transporting it to sites of DNA damage in the nucleus. The interaction between the BRCA1 protein and the RAD51 protein is less clear, although research suggests that BRCA1 may also activate RAD51 in response to DNA damage. By helping repair DNA, these three proteins play a role in maintaining the stability of a cell's genetic information. High Grade Serous Ovarian cancer is most lethal gynecological malignancy, which necessitates further research into potential therapy targets. Because of its integral role in double strand break repair, an abnormal RAD51 protein may contribute to the mutation of an oncogene. RAD51 is a critical recombinase and necessary component for a functional homologous recombination (HR) repair pathway. Hence, by selectively degrading RAD51 in tumor tissue with targeted therapy we will be able to induce HR deficiency, which can then be combined with PARP inhibitors to achieve tumor-specific therapeutic outcomes. Since RAD51 is a bona fide therapeutic target in Ovarian Cancer, RAD51-targeting molecules would be excellent for use as single agents or in combination with conventional chemotherapy.

Experimental Procedures: To determine the extent to which ovarian cancer cells exhibit acquired dependency of RAD51, we first assessed RAD51 expression in three ovarian cancer cell lines, COV318, OVSAHO, and ONCO-DG1. Using western blotting we observed a robust expression of RAD51 in all three cell lines. We then used siRNA gene silencing technology to knock down RAD51 expression in these cancer cell lines and determined cell viability following the knockdown using the Cell-TiterGlo cell viability assay. These results suggest RAD51 targeting produces beneficial therapeutic effects in ovarian cancer. We also used viral transduction to generate three ovarian cancer cell lines that express RAD51 (HeLa, OVSAHO, ONCO-DG1) to serve as cell line models to screen for drugs that degrade RAD51 in cancer cells.

Summary of Data: Our data indicates that ovarian cancer cells exhibit acquired dependencies on RAD51 expression because RAD51 knockdown results in decreased cell viability and increased cell death.

Conclusion and Significance: Further research is needed to determine if RAD51 is an oncogene. Additionally, the cytotoxicity of RAD51 knockdown should be tested in other types of cancer. However, because a RAD51 knockdown leads to cell death in these ovarian cancer cell lines, it follows that RAD51 could be a potential target of future cancer therapy studies.

<<30>> THE EFFECT OF GERMLINE POLYMORPHISMS ON SOMATIC HOTSPOT MUTATIONS IN *TP53* IN CANCER

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Introduction: Epithelial ovarian cancer (EOC) ranks first in mortalities associated with gynecological malignancies and exhibits different histopathological patterns giving rise to different disease outcomes. Even with current treatment modalities of surgical debulking and chemotherapy, the overall prognosis is relatively poor with a 5-year survival rate of 45%. High-grade serous ovarian carcinomas (HGSOC) are the most common subtype of EOC and feature almost universal *TP53* mutation patterns. The Cancer Genome Atlas (TCGA) has provided key insight into molecular alterations that are common in ovarian tumors. Of note, mutations in a single gene, *TP53*, were identified in 96% of all serous ovarian tumors. *TP53* encodes the tumor suppressor protein p53, which acts as a major control center in the cellular response to various stress such as DNA-damaging chemotherapy and activates in response to cellular stress. *TP53* is a tumor suppressor gene that undergoes biallelic inactivation by deletions, truncations and in a majority of cases (74%) monoallelic missense mutations that are present in hotspot regions of the DNA binding domain of the protein thus abrogating its DNA binding activity. Most mutations within the *TP53* gene are missense, introducing single amino acid changes at different positions of the protein. A frequent variant also exists within the *TP53* gene concerning a polymorphism at codon 72, encoding either proline (P) (Pro72;CC) or arginine (R) (Arg72;GG) P72R. Of the 19 validated coding germline polymorphisms that have been identified in *TP53*, the P72R polymorphism has been widely studied with an emphasis on the differential effect of this polymorphism on wildtype function of *TP53*. Using a pan-cancer sequencing dataset from the Cancer Genome Atlas and multiple *in-vitro* and *in-vivo* studies we have determined the association between somatic mutations and the P72 or R72 allele.

Experimental Procedures: Using bioinformatic analysis on the pan cancer sequencing dataset from The Cancer Genome Atlas (TCGA) of around 13,000 cancer patients, we identified 4000 cases with somatic mutations in *TP53*, and found 409 patients with the heterozygous P72R germline polymorphism. We also validated the effect of negative selection of the P72 polymorphism with missense mutations in *TP53* using immunoblotting, immunofluorescence, flow cytometry analysis, RNA-sequencing, Chromatin Immunoprecipitation and orthotopic mouse models.

Summary of Data, Conclusion and Significance: Our results suggest that the P72R germline polymorphism affects the allelic selection of somatic mutants in *TP53*. Our results also point to an alternative mechanism as to why the R72 allele is preferentially enriched in tumor samples and the P72 allele undergoes a negative selection. Our studies indicate that the P72 allele could be regulating either cell death apoptotic pathways or cell cycle arrest pathways whereas the R72 allele loses all canonical *TP53* tumor suppressor activity thus promoting cancer development. It is important to note that both positive selection of mutants with R72 polymorphism and the negative selection of mutants with P72 polymorphism could play a role in the development of cancer. Consequently, germline polymorphisms like P72R can either attenuate the detrimental effects of mutant p53 or partially rescue the loss of function p53 mutants. With this approach in mind, cancer treatment for patients with specific combinations of somatic mutations and germline polymorphisms can be designed that offer a specific and targeted approach to overcome the detrimental effects of *TP53* dysfunction. This phenomenon is identified in a variety of cancer types which ensures a global, population specific approach to target aberrant p53 pathways in cancer treatment and ensure disease free survival.

<<31>> EFFECTIVENESS OF ETRAVIRINE AND SUNITINIB-BASED THERAPY FOR CELL LINES RESISTANT TO ER STRESS

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Introduction: Recently our group has reported on the mechanism of resistance towards Valosin-containing protein (VCP) inhibitors (Bastola, Chien et al). Valosin-containing protein VCP (p97; cdc48 in yeast) is a hexameric, type II ATPase of the AAA family (ATPases with multiple cellular activities) that mediates disparate cellular functions, including endoplasmic reticulum-associated degradation (ERAD) via the ubiquitin-proteasome system (UPS). We have previously used HCT-116 colon cancer cells to generate cells that are resistant to a VCP inhibitor CB5083 (CB) and have shown that this resistance is due to a mutation in the VCP

gene. To overcome this resistance to CB, we performed a drug screen in CB-resistant cells using FDA-approved drugs.

Experimental Procedures: Using parental and CB-resistant (CB9) HCT-116 colon cancer cells, we performed a single-dose (5 uM) drug screen consisting of approximately 400 drugs to identify those that showed enhanced cytotoxic effects in CB9 cells. After identification of initial hits, we treated the parental and resistant cells with candidate hits at varying concentrations ranging from 0-10 µM and performed dose-response studies using CellTiter-Glo. To avoid experimental error all experiments were conducted in at least three technical replicates and three independent experimental replicates. We further validated our results using long term assays like the clonogenic assay at the same concentration ranges.

Summary of Data: Our initial single-dose drug screen identified etravirine (ETR) as a candidate hit that showed enhanced cytotoxicity in CB9 cells compared to parental cells. Our dose-response studies show that ETR has a significantly higher IC_{50} in HCT116 parental cells relative to CB9 cells, thus indicating that etravirine may be active against CB-resistant cells. Our results also indicate that CB resistant cells have fewer colonies compared to the HCT-116 parental colonies upon ETR treatment. ETR is an orally administered second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI). It is prescribed for the treatment of HIV-1 and is one of the key drugs of highly active antiretroviral therapy (HAART) in the clinical management of acquired immune deficiency syndrome (AIDS). We also evaluated the efficacy of FDA approved tyrosine kinase inhibitor Sunitinib which is used to treat metastatic renal cell carcinoma (mRCC). Sunitinib inhibits multiple receptor tyrosine kinases (RTKs), especially those involved in angiogenesis, such as vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and proto-oncogene cKIT. Our results indicate that upon Sunitinib treatment there was no significant difference in the IC_{50}'s between the HCT-116 parental cells and the CB-9 cells thus indicating that there is a comparable cytotoxic effect induced by Sunitinib on both CB resistant and CB sensitive cells.

Conclusion and Significance: Although resistance to CB is rapidly acquired *in vitro*, resistant cells acquire new dependencies that can be exploited with HIV drug etravirine. Future studies are needed to determine the mechanism behind the effect of etravirine on colorectal carcinoma cell lines. Colorectal carcinoma is the third most common and fourth most lethal type of cancer thus warranting an immediate need for developing new therapeutics that can overcome existing resistance mechanisms in cancer cells. There is an abundance of information on etravirine's efficacy as a treatment for HIV-1; however, its effect and mechanism of action on cancer cells is unknown. Although our studies identified etravirine as a potential drug for CB9 cells, the extent to which etravirine is also active against other CB-resistant cells is not known. Nonetheless, the results from our study are significant because they illustrate acquired dependencies in CB9 cells that can potentially be exploited with other drugs; thus, opening new avenues for drug development and improving therapeutic index for CB-resistant cells.

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<<32>> ANALYSIS OF TIGAR EXPRESSION ACROSS A PANEL OF OVARIAN CANCER CELL LINES AND ORGANOID SAMPLES

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Introduction: *TIGAR* (*TP53* Inducible glycolysis and apoptosis regulator) located on the chromosomal region 12p13.32 is encoded by the *C12orf5* gene. This gene is regulated as part of the p53 tumor suppressor pathway and encodes a protein with sequence similarity to the bisphosphate domain of the glycolytic enzyme that degrades fructose-2,6-bisphosphate. Our group has previously published data indicating *TIGAR* knockdown decreases NAD+ precursor nicotinic acid and NADP+ and NADPH, increases intracellular reactive oxygen species level, decreases the nucleobase pool and inhibits cell growth by causing DNA replication stress, delaying S-phase progression, and inducing senescence. Our previous studies have thus shown that *TIGAR* is a relevant therapeutic target to explore as mono or combination therapies for treating cancers. This

protein functions by blocking glycolysis and directing the pathway into the pentose phosphate shunt. Expression of this protein also protects cells from DNA damaging reactive oxygen species and provides some protection from DNA damage-induced apoptosis. In order to further investigate the role of TIGAR within specific cancerous cell growths, we used a panel of ovarian cancer cell lines and ovarian organoid samples to quantitatively measure gene expression and determine a link between TIGAR expression and cancer cell proliferation.

Experimental Procedures: Total RNA was extracted with the Trizol reagent (15596-028, Invitrogen) according to the manufacturer's manual. The cDNA was synthesized using SuperScript II reverse transcriptase (180604014, Invitrogen) with 1 µg of total RNA in a 20 µL reaction. The resulting cDNA was diluted 1:20 in nuclease-free water and 1 µL was used per qPCR reaction with triplicates. To find the optimal annealing temperature for *TIGAR* a gradient-PCR was performed first . The qPCR was carried out using Power SYBR Green PCR Master Mix (4367659, Thermo Fisher Scientific) on a CFX96 Real-Time PCR Detection System (Bio-Rad) including a non-template negative control. Amplification of 18S rRNA was used to normalize the level of TIGAR mRNA expression. Quantitative PCR was performed on all 15 cell lines and organoid samples.

Summary of Data: The *TIGAR* gene, when quantitatively analyzed, indicated differential expression levels where in some patient derived organoid samples, TIGAR expression was significantly higher in organoids at day 6 relative to organoids at day 0. However, some organoids did not indicate a significant difference in TIGAR expression when compared between Days 0 and 6 respectively. Also, TIGAR expression levels vary between different ovarian cancer cell lines thus indicating that some cell lines could have a higher dependence on TIGAR for cell survival and growth relative to their counterparts.

Conclusion and Significance: Recent studies show *TIGAR* promotes cell proliferation in certain cancers such as glioma, multiple myeloma, and colorectal cancer and thus is a novel target for both clinical diagnosis, gene therapy and treatment with therapeutics like PARP inhibitors in addition to conventional chemotherapeutics. After analyzing its role in ovarian cancer cells and determining that *TIGAR* is significantly overexpressed in multiple tissue samples, *TIGAR* is presented as a novel candidate for cancer therapy.

<<33>> TRANSCRIPTOMIC CHARACTERIZATION OF 2D AND 3D *IN VITRO* MODELS OF PANCREATIC DUCTAL ADENOCARCINOMA UNDER HYPOXIA

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Pancreatic cancer is one of the deadliest solid malignancies, with little improvement in survival rates in three decades. Hypoxia is an important characteristic of the microenvironment in pancreatic cancer, which plays critical roles in cancer proliferation, metastasis, and therapy response. In this project, we characterize the transcriptomic profile of several commonly used *in vitro* models of pancreatic cancer, namely six 2D cell lines and three 3D organoid lines. Recently developed organoid models hold great promise for exploring the biology of cancer, personalized medicine, and drug development. The extent and nature of the response of cell lines to hypoxia was found to be heterogeneous. Therefore, we concluded that biological insights from studying any one cell line ought to be generalized with caution. Organoids showed a broad transcriptomic response to hypoxia, via upregulation of pathways such as HIF-1 signaling, glycolysis, angiogenesis, and migration, and downregulation of genes involved in biological processes such as cell division, DNA replication, and DNA repair. Cobalt Chloride (CoCl2), a commonly used chemical model of hypoxia, was found to be an overall insufficient and unreliable proxy for mimicking the transcriptomic response to true hypoxia in both cell lines and organoids. Organoids grown under hypoxia appear to degrade the Matrigel support, likely due to extracellular modification. To grow organoids under hypoxia, a suitable supporting matrix will be needed.

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preparation, RNA sequencing, and data analysis. Allen Gao's laboratory in UCD Department of Urology, Alan Lombard and Leandro D'Abronzo, for their assistance with western blots.

<<34>> XY018 FOR THE TREATMENT OF MUSCLE INVASIVE BLADDER CANCER.

Christopher Lucas

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Bladder cancer will account for an estimated 17,670 deaths from cancer and 80,470 new cancer diagnoses in the United States in 2019. The general 5-year survival rate is 77% but this includes low stage disease (non-muscle invasive) which has a 5-year survival of 95%. Once the disease has progressed to high stage disease, the survival rate drops significantly down to 35% for those with lymph node involvement or metastasis. Current treatment options for high stage invasive bladder cancer are limited in scope and effectiveness, with only a single year of survival extension. Cbioportal analysis has revealed that ROR gamma, a member of the nuclear receptor family, is overexpressed and amplified in bladder malignancies. ROR-gamma is already a drug target for human autoimmune diseases and as such lends itself for targeting within bladder cancer. XY018 has shown great potential in prostate cancer cells, functioning as a ROR-gamma antagonist and inducing apoptosis. We used proliferation and apoptosis assays to confirm that administering XY018 in six different bladder cancer cell lines resulted in apoptosis. Western blot analysis confirmed that ROR-gamma was reduced in cell lines treated with XY018 when compared with a control group. *In vivo* studies used the BI-0440 PDX tumor to test efficacy of XY018 within a model organism. The PDX tumors showed no significant difference in growth determined by tumor mass, volume and model organism survival when compared with control organisms. Western blot analysis of lysed tumor samples showed no difference in ROR-gamma expression as had been seen in cell culture assays. While XY018 ROR-gamma inhibition effectively limited cellular viability of multiple bladder tumor cell lines, it was not effective in reducing the growth of the BI-0440 bladder PDX tumors. Potential future directions included experiments to better understand the possible reasons of lack of efficacy, including an in vitro examination of the inhibitor efficacy using tumor organoids derived from this PDX, and alternatively study RORgamma inhibitors using the mouse MB49 cells-derived tumors in syngeneic, immunocompetent mice, with the objectives to determine whether the RORgamma inhibitor alone or in combination with a specific immune checkpoint blocker can elicit a strong tumor inhibition and the possible involvement of tumor immune microenvironment.

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<<35>> TUMOR SUPPRESSOR p14ARF DEPLETION PROMOTES APOPTOSIS IN PROSTATE CANCER CELLS

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One hallmark of prostate cancer PCa is its exquisite dependence on optimal activity of the androgen receptor (AR) where physiological androgen concentrations induce proliferation but castrate and supraphysiological levels suppress PCa growth. This feature has been exploited in bipolar androgen therapy (BAT) for castrate resistant malignancies. PCa malignancies also have defects in the p53 tumor suppressor signaling and there is an interplay between AR and p53 pathway components. We used a tumor tissue array of differing stages and grades to define the relationships between these components by assessing their expression in the nuclear and cytoplasmic compartments of tumor and adjacent cells. Multivariate analysis identified a strong positive correlation between p14ARF and AR expression. Mechanistic studies utilizing CWR22 xenograft and cell culture models revealed that castrate androgen levels or AR depletion reduced p14ARF expression and deregulated E2F factors linked to p14ARF and AR regulation. Chromatin immunoprecipitation studies identified androgen sensitive AR binding sites upstream of p14ARF. p14ARF depletion enhanced AR-dependent PSA and TMPRSS2 transcription arguing that p14ARF constrains AR activity. Elevation of AR activity was accompanied by a decrease in cell viability, decreased E2F1, 2 expression, and increased CDK inhibitor p27 levels, however, longer p14ARF depletion resulted in apoptosis. In the context of prostate cancer cells, AR co-

ops p14ARF as part of a feedback mechanism to ensure optimal AR activity for maximal prostate cancer cell survival and proliferation.

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<<36>> SAFETY AND EFFICACY OF A NOVEL IMMUNOTHERAPY STRATEGY INCORPORATING EPACADOSTAT, INTRALESIONAL SD-101, AND RADIOTHERAPY DEMONSTRATING ACTIVITY IN CHECKPOINT REFRACTORY PATIENTS

James Liu, Christina Poh, Jingran Ji, May Cho, Xiao Zhou, Mehrdad Abedi, Joseph Tuscano, Edward J. Kim, Karen Kelly, Helen Chew, Mamta Parikh, Mili Arora, Shyam Rao, Megan E. Daly, Ghaneh Fananapazir, Sima Naderi, Thomas Loehfelm, Robert J. Canter, Michael S. Kent, William J. Murphy, Arta M. Monjazeb

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Background: The efficacy of tri-modality immunotherapy strategy (intralesional TLR9 agonist, local radiotherapy, and IDO blockade) was previously demonstrated in mouse models and canines with spontaneous malignancies. Published clinical studies suggest a strong in-situ vaccination effect of combining TLR agonists and radiotherapy.

Methods: IRB approved protocol UCDCC #271 (NCT03322384) a phase I/II clinical trial of epacadostat, intralesional SD-101 (4mg x 5 weekly injections), and local radiotherapy (2Gy x 2, 4Gy x 5, or 8Gy x 3) for patients with advanced refractory solid tumors (cohort 1) and lymphomas (cohort 2) opened to accrual in 4/2018. The trial was designed as a phase I 3+3 dose de-escalation starting at 300 mg po bid of epacadostat. The phase II was designed as a simon-two stage expansion for each cohort.

Results: To date 19 patients have accrued this study. Benefit of therapy was experienced by 5/14 evaluable patients and response was observed in 2/16 patients. Across both cohorts 10 patients were refractory to prior therapy with PD-(L)1 checkpoint inhibition. Benefit of therapy was seen in 3/10 of these patients including 1 sustained near CR and 1 sustained CR.

Conclusions: This is the first in human report of this novel triple therapy strategy and the first in human report of visceral intralesional injections of SD-101. Treatment was well tolerated and demonstrated activity in both lymphomas and solid tumors.

<<37>> TREATMENT PATTERNS AND SURVIVAL IN VERY ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA, A POPULATION-BASED STUDY

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. Approximately half of cases occur after age 70. R-CHOP is the standard of care, but toxicity concerns can limit its use in the very elderly (>80 years), a group with a growing population and an increasing incidence of the disease. Understanding treatment patterns and associated survival can help determine effective management strategies in this population.

Methods: Data for 17,859 patients ages ≥65 diagnosed with DLBCL from 2006 to 2017 were obtained from the California Cancer Registry (CCR). Detailed treatment information for each patient was extracted from treatment text fields in the CCR. Multivariable logistic regression models examined characteristics associated with no treatment while multivariable cox proportional hazards regression models examined the influence of treatment on overall survival. Models were adjusted for insurance, race/ethnicity, neighborhood socioeconomic status (nSES), comorbidity score, rural/urban location, year of diagnosis, initial treatment at National Cancer

Institute (NCI)-designated cancer center, stage at diagnosis, sex, and age. Results are presented as adjusted odds ratios (OR) and adjusted hazard ratios (HR) with 95% confidence intervals (CI).

Results: Sixty-seven percent of patients were ages 65 to 80 while 33% were >80 years. Across both age groups, the most common regimen was R-CHOP (36%), followed by CHOP (5.6%), R-EPOCH (3.1%), mini-CHOP with or without R (1.0%), and EPOCH (0.3%). Other drug combinations comprised a large proportion of the treatments (27%); 19.8% of patients had unknown treatment. For patients >80, fewer received R-CHOP (21%), more received other drug combinations (31%), and more had no treatment (13%) than those ages 65-80 (43% R-CHOP, 25% other combinations, 5% no treatment). Factors associated with no treatment in patients >80 included greater comorbidity (OR: 1.57, CI: 1.28, 1.93), more recent years of diagnosis (OR: 1.37, CI: 1.10, 1.70 for 2014-2017, vs 2006-2009), initial treatment at non-NCI designated cancer centers (OR: 2.72, CI: 1.91, 3.89), and female sex (OR: 1.24, CI: 1.06, 1.46). Among patients >80, survival was decreased for patients receiving other drug combinations (HR: 1.51, CI: 1.38, 1.66) and no treatment (HR: 3.29, CI: 2.95, 3.68) compared with R-CHOP. Other factors associated with worse survival included low nSES, increasing comorbidity, treatment at non-NCI designated center, and increasing stage at diagnosis.

Conclusion: In this large population-based group of elderly patients with DLBCL, we observed that very elderly (>80) patients were less likely to receive initial treatment and more likely to receive other drug combinations despite a survival advantage with standard regimen protocols. Further analysis examining patient comorbidities and treatment-related toxicities are warranted.

NOTES

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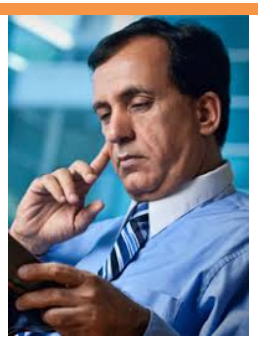
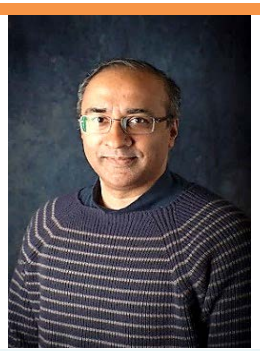
Cancer Biology Research Seminars Fall 2019

Thursdays	September 26	October 10	Nov 14	Nov 21	December 12
9am-10am UC Davis Comprehensive Cancer Center					
	Surinder K. Batra, M.D. Ph.D.	Amina Zoubeidi, Ph.D.	Sridhar Mani, MD	Dr. Yang-Xin Fu	Dipak Panigraphy, M.D.
4501 X Street Sacramento	University of Nebraska Medical Center	Vancouver Prostate Center	Einstein University	UT Southwestern University	Harvard University
CBS Faculty Coordinator: Kermit Carraway, PhD klcarraway@ucdavis. edu	"Current Status of MUC4 in the Diagnosis and Therapy of Pancreatic Cancer"	"Cellular Plasticity in Treatment Resistant Prostate Cancer"	" From Nuclear Receptors to Microbes: Unexpected Cross Roads"	"Radiation-Induced Innate Sensing for Immunotherapy"	The overall goal of the Panigrahy laboratory is to elucidate the mechanisms by which eicosanoids such as EETs can stimulate tumor growth. Understanding the role of eicosanoids in tumorigenesis is of direct clinical relevance as the pharmacologically accessible autacoids system, such as EETs, may offer an entirely new system of targets for anti-stromal and anti-angiogenesis strategies in cancer therapy.
Light Refreshments served	UCD Host: Paramita Ghosh, Ph.D.	UCD Host: Paramita Ghosh, Ph.D.	UCD Host: Aiming Yu, Ph.D.	UCD Host: Jian Jian Li, M.D.	UCD Host: Bruce Hammock, Ph.D. Paul Henderson, Ph.D.

Trans-Center Themes

Cancer Risk Mitigation and Early Detection	Innovative Cancer Models and Technologies	Precision Therapeutics and Transformative Imaging

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