21st Annual Cancer Research Symposium

October 29–30, 2015

Comprehensive Cancer Center Auditorium
4501 X Street, Sacramento
Courtyard by Marriott Hotel
4422 Y Street, Sacramento

~ Breaking Barriers to Beat Cancer ~
Welcome to our 21st annual symposium, an event that has allowed us to bring many outstanding speakers to our campus. It has allowed us to introduce new faculty to everyone and has been the springboard for many fruitful interactions, this year is no exception. However, this year also marks our resubmission of our core grant, which is a process that takes place every five years.

Currently, we are preparing for the Site Visit in March of next year. Over the next two days, we will have a chance to showcase some of the themes that will be presented to peer review come March 1, 2016. The focus is on bringing better health care to our patients and family, both that we see at UC Davis Comprehensive Cancer Center but also within our broader community. Our efforts are to reduce mortality from cancer health disparities and improve survival from advanced disease through genomics immunotherapy.

To all of you, thank you so much for all you have contributed throughout 2015 and indeed the last 20 years to our Cancer Center, to allow us together to meet our mission and push forward in creating and disseminating new knowledge in helping to break barriers to beat cancer.

All the best,

Ralph W. de Vere White, M.D.
Director, UC Davis Comprehensive Cancer Center
Associate Dean for Cancer Programs
Codman-Radke Chair in Cancer Research
Distinguished Professor, Department of Urology
SYMPOSIUM COMMITTEE MEMBERS

Ralph de Vere White, MD
Director, UC Davis Comprehensive Cancer Center (UCDCCC)
Assistant Dean for Cancer Programs
Distinguished Professor, Department of Urology

Wolf-Dietrich Heyer, PhD
Molecular Oncology Program leaders, UCDCCC
Chair, Department of Microbiology and Molecular Genetics
Professor, Microbiology and Molecular Genetics

Primo “Lucky” Lara, MD
Associate Director for Translational Research, UCDCCC
Professor, Division of Hematology and Oncology

Karen Kelly, MD
Associate Director for Clinical Research, UCDCCC
Professor, Department of Hematology and Oncology

Moon Chen, MPH, PhD
Associate Director, Population Research and Cancer Disparities, UCDCCC
Professor, Department of Hematology and Oncology

Marcio Malogolowkin, MD
Chief, Division Pediatric Hematology and Oncology, UC Davis Medical Center

SYMPOSIUM STAFF

Melanie Bradnam, PhD; Gina Dayton; Sonal Desai, PhD; Edson Kong; John D. Perez, MCM; Francis De La Cruz - UC Davis Comprehensive Cancer Center

SPECIAL THANKS

For over two decades of amazing physicians, scientists, staff and volunteers who have helped build the Cancer center from opening day in 1991 to our designated Comprehensive status. Without your team efforts we would not be here today.
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<tr>
<td>8:30-8:40 am</td>
<td>Introduction and Welcome</td>
<td>Wolf-Dietrich Heyer, PhD, UCDCCC</td>
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<td>8:40-9:20 am</td>
<td>Challenges of Pediatric Cancer Clinical Research – Pediatric Liver Tumors</td>
<td>Marcio Malogolowkin, MD Div. Pediatric Hematology Oncology</td>
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<td>a Model of Clinical Research and International Cooperation (Keynote)</td>
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<td>9:20-9:40 am</td>
<td>Impact of Treatment and Insurance on Socioeconomic Disparities in Survival</td>
<td>Theresa Keegan, MS, PhD Div. Hematology and Oncology</td>
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<td>After Adolescent and Young Adult Hodgkin Lymphoma: A Population-Based Study</td>
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<td>9:40-10:00 am</td>
<td>Childhood Cancer Survivorship</td>
<td>Kathryn Wells, MS, CPNP, CPON Div. Pediatric Hematology Oncology</td>
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<td>10:00–10:20 am</td>
<td>Development of Novel Targeted Therapies for Children's Cancers: Monoclonal</td>
<td>Noriko Satake, MD Dept. Pediatrics</td>
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<td>Antibody Conjugates with Antisense Oligonucleotide</td>
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<td>10:20-10:40 am</td>
<td>Lessons Learned from Histone Mutations in Pediatric Gliomas</td>
<td>Ben Yuen Dept. Cell. Biol &amp; Human Anatomy</td>
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<td>10:40–10:50 am</td>
<td>Break</td>
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<td>10:50–11:10 am</td>
<td>Taking Cues from Cancer Cures for HIV Eradication</td>
<td>Satya Dandekar, PhD Dept. Medical Microbiol and Immunol</td>
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<td>11:10–11:30 am</td>
<td>The Genomic Landscape of Canine Glioma</td>
<td>Kevin Woolard, DVM, PhD Dept. Pathol, Microbiol and Immunol</td>
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<td>11:30–11:50 am</td>
<td>Association of Raccoon polyomavirus with Neuroglial Tumors</td>
<td>Patricia Pesavento, DVM, PhD Dept. Pathol, Microbiol and Immunol</td>
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<td>11:55–1:45 pm</td>
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**SESSION II – Re-defining Bench-to-Bedside**

*Chair: David R. Gandara, MD*

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<td>1:50–2:50 pm</td>
<td>The BAP1 Cancer Syndrome: Mesothelioma, Melanomas, Carcinomas and Sarcomas</td>
<td>Michele Carbone, MD, PhD University of Hawaii Cancer Center Div. Clinical and Cancer Prevention (Keynote)</td>
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<td></td>
<td>Causes, Mechanisms and Clinical Implications</td>
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<td>Cancer Drug &amp; Biomarker Development</td>
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<td>3:10–3:30 pm</td>
<td>SPIDER: Serial Patient derived xenograft moDelis to Eliminate cancer therapy</td>
<td>Thomas Semrad, MD, MAS Div. Hematology and Oncology</td>
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<td>3:30–3:40 pm</td>
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<td>3:40–4:00 pm</td>
<td>Strategies to Achieve Better Outcomes for Patients With Urothelial Carcinoma</td>
<td>Chong-xian Pan, MD, PhD Div. Hematology and Oncology</td>
<td>Cancer Center Auditorium</td>
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<td>4:00–4:20 pm</td>
<td>Blocking Indolamine-2,3-Dioxygenase Rebound Immune Suppression Boosts Anti-tumor</td>
<td>Arta Monjazeb, MD, PhD Dept. Radiation Oncology</td>
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<td>Effects of Radio-Immunotherapy in Murine Models and Spontaneous Canine Malignancies</td>
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<td>4:20–4:40 pm</td>
<td>Phase I Evaluation of Nanomicelle Encapsulated Doxorubicin in Dogs with Lymphoma</td>
<td>Jenna Burton, DVM, MS Dept. Surgical and Radiological Sciences</td>
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<td>4:40–5:00 pm</td>
<td>Expanding Our Senses: Novel Diagnostic Technologies From German Lasers to German Shepherds</td>
<td>Gregory Farwell, MD, FACS Dept. Otolaryngology</td>
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<td>8:30–9:10 am</td>
<td>Molecular Imaging at UC Davis</td>
<td>Julie Sutcliffe, PhD&lt;br&gt;Dept. Biomedical Engineering</td>
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<td>9:10–9:50 am</td>
<td>The EXPLORER Total Body PET Scanner Program at UC Davis (Keynote)</td>
<td>Terry Jones, DSc&lt;br&gt;Visiting Professor, UC Davis; Co-Director PET Research Advisory Company</td>
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<td>9:50–10:10 am</td>
<td>Quantitative Kinetic Modeling Approaches for Human Molecular Imaging Studies</td>
<td>Guobao Wang, PhD&lt;br&gt;Dept. Biomedical Engineering</td>
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<td>10:10–10:20 am</td>
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<td>10:20–10:40 am</td>
<td>Microfluidic culture Systems Used to Study Paracrine and Autocrine Signals in the Cancer Microenvironment</td>
<td>Alex Revzin, PhD&lt;br&gt;Dept. Biomedical Engineering</td>
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<td>10:40–11:00 am</td>
<td>A Theranostic Nanoporphyrin Platform</td>
<td>Yuanpei Li, PhD&lt;br&gt;Dept. Biochem and Mol Medicine</td>
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<td>11:00–11:20 am</td>
<td>Fluorescence Lifetime Techniques in Clinical Interventions</td>
<td>Laura Marcu, PhD&lt;br&gt;Dept. Biomedical Engineering</td>
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<td>11:25–1:15 pm</td>
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**SESSION IV – UC Davis Human Cancer Genomics Program**

*Chair: John McPherson, PhD*

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<td>Promises and Pitfalls of Cancer Genomics (Keynote)</td>
<td>John McPherson, PhD&lt;br&gt;Dept. Biochem and Mol Medicine</td>
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<td>2:00–2:20 pm</td>
<td>A Population-Based Study of Highly Penetrant Genes Finds That One in Four Young Hispanic Women with Breast Cancer Carry BRCA1/2 or PALB2 mutations</td>
<td>Anna Marie Tuazon&lt;br&gt;Dept. Biochem and Mol Medicine</td>
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<td>2:20–2:40 pm</td>
<td>Molecular Oncology Tumor Board</td>
<td>Karen Kelly, MD&lt;br&gt;Div. Hematology and Oncology</td>
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<td>2:40–3:00 pm</td>
<td>Clinical Trial Using Bioengineered Stem Cells to Treat HIV Patients Suffering From Lymphoma</td>
<td>Mehrdad Abedi, MD&lt;br&gt;Div. Hematology and Oncology</td>
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Symposium Close
ORAL PRESENTATIONS

UC Davis Comprehensive Cancer Center Auditorium
4501 X Street, Sacramento

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Marcio Malogolowkin, MD
Chief, Division Pediatric Hematology-Oncology, UC Davis Medical Center

Dr. Malogolowkin completed his medical training at The Medical School of Federal University of Rio de Janeiro, Brazil, and began his career in pediatric oncology as a fellow at Children’s Hospital Los Angeles, where he served as medical director and later division head for clinical affairs and clinical research. Before coming to UC Davis, Malogolowkin led the hematology, oncology and bone marrow transplant program at Children’s Hospital of Wisconsin. While there, Malogolowkin contributed to the improvement of treatment for liver tumors. He identified patients who could be cured with surgery alone and improved overall survival to greater than 80 percent for patients receiving chemotherapy while decreasing long-term treatment toxicity.

Treating children with cancer for more than 29 years, Dr. Malogolowkin is passionate about developing new therapeutic approaches to improving outcomes and quality of life for his patients, with a specific focus on pediatric rare tumors. Throughout his career he has developed and conducted numerous institutional studies that have gone on to serve as the basis for national studies in the area of treatment of liver tumors, metastatic sarcomas and recurrent Wilms tumors. Previous work has included the development of protocols (which included autologous BMT) for patients with metastatic sarcomas, chemoembolization for unresectable/recurrent liver tumors, new therapeutic approaches for recurrent Wilms tumor, and intensification of therapy for children with high-risk germ cell tumor. He has participated in the development of new therapeutic approaches for these tumors, and fostered national and international collaboration for biology and therapeutic studies.
Dr. Michele Carbone, MD, PhD
Professor of Pathology and the Director of Thoracic Oncology at the University of Hawaii Cancer Center.

Dr. Carbone worked at the National Institutes of Health (NIH) from 1986 to 1994, at the University of Chicago and Loyola University Cancer Center of Chicago from 1994 until 2006, when he joined the University of Hawaii. From 2007 till 2009 he served as Chair of the Department of Pathology at the University of Hawaii Medical School. From 2009 to 2014 he served as the Director of the University of Hawaii Cancer Center.

Dr. Carbone studied mechanisms of asbestos carcinogenesis and found that SV40, a virus that contaminated polio vaccine, synergizes with asbestos in causing mesothelioma. He studied an epidemic of mesothelioma in Cappadocia, Turkey, and demonstrated the existence of a genetic susceptibility factor. Following up on that research, Dr. Carbone studied US families with high incidence of mesothelioma and he discovered a new cancer syndrome that linked BAP1 germline mutations to the development of mesothelioma, uveal melanoma and other cancers. His discoveries of extensive erionite exposure in North Dakota, U.S., and anthophyllite asbestos in Nevada, led to cancer preventive measures and social and community improvements. In parallel studies, Dr. Carbone in collaboration with Dr. Haining Yang, studied the role of HMGB1-driven inflammation in the pathogenesis of mesothelioma.

Dr. Carbone has published over 150 peer-reviewed papers. His research has been funded through grants from the National Cancer Institute, the American Cancer Society and the V-Foundation. In 2008, he received the AACR-Landon Innovator Award for International Collaboration in Cancer Research and, in 2014, the Mesothelioma Applied Research Foundation conferred its Pioneer Award on Dr. Carbone. Dr. Carbone has the honorary title of Knight of the Republic of Italy for his achievements in science and medicine.
Terry Jones, DSc
Visiting Professor, Department of Radiology, UC Davis; Director, PET Research Advisory Company

Dr. Jones is a medical physicist who, when at the former MRC Cyclotron Unit, initiated the United Kingdom’s first PET program. He undertook a number of developments in PET methodology which included collaborations with industrial manufacturers of PET scanners. He was awarded an MRC travelling fellowship in 1972 to work at the University of Washington St Louis and the MGH in Boston which led to demonstrating the first image of the human brain metabolism. Together with medical colleagues at the Royal Postgraduate Medical School at Hammersmith Hospital, he fostered the research applications of PET methodology in neurology, psychiatry, oncology, cardiology and pulmonary medicine. To support pre-clinical studies, he established the world’s first dedicated small–animal PET scanner. At the MRC Cyclotron Unit he rose to the position of Acting Director and Professor of Medical Physics at Imperial College London. He then went on to establish the state-of-the-art PET based Wolfson Molecular Imaging Centre at Manchester University where he was Professor of Molecular Imaging. He is currently co-director of the PET Research Advisory Company, visiting professor at the University of California, Davis and visiting senior scientist at the Imanova Centre for Imaging Sciences London.

Dr. Jones has over 290 publications related to PET methodology and applications. His role on this proposal is to provide critical input and advice on each stage of the proposed methodology development, bringing his expertise to bear on any challenges encountered, and helping the EXPLORER consortium recognize the opportunities for this system in clinical research using his extensive network of connections in the academic PET community.
KEYNOTE SPEAKER BIOGRAPHICAL INFORMATION

John McPherson, PhD
Associate Director for Basic Sciences and Deputy Director, UC Davis Comprehensive Cancer Center; Professor, Department of Biochemistry and Molecular Medicine, UC Davis.

Dr. McPherson recently joined the UC Davis Comprehensive Cancer Center as Deputy Director and Associate Director for Basic Sciences (Department of Biochemistry and Molecular Medicine). His prior appointment was Director, Genome Technologies at the Ontario Institute for Cancer Research (OICR; 2007-2015), where he ran a next-generation sequencing program aimed at deciphering cancer genomes. As a founding member of the International Cancer Genome Consortium, the OICR targeted large-scale analysis of pancreas and prostate tumors in addition to multiple smaller projects in other cancer types. Dr. McPherson interests lie in understanding the mechanisms underlying structural rearrangements in tumors and in bringing advanced genomic technologies to clinical application in personalized diagnosis and targeted therapeutics through maximizing the data yield from small biopsies and circulating cell free DNA.

Dr. McPherson’s career also previously spanned three Genome Centers: as Co-Director, the National Human Genome Research Centre - Chromosome 5 Genome Center (1993-1996); as Co-Director, the Washington University Genome Sequencing Center (WU; 1996-2003); and as Senior Faculty, the Human Genome Sequencing Center at the Baylor College of Medicine (BCM; 2003-2007). At WU he pioneered many large-scale mapping and sequencing technologies and was the lead author on the human genome physical map, co-published with initial draft sequence of the human genome; and at BCM he established an early high-throughput targeted resequencing pipeline with a peak capacity of one million Sanger sequences per month of PCR amplified genome targets. The primary objective of the BCM pipeline was the sequencing of all ion channel genes (~250) in 500 sporadic epilepsy patients and controls. This pipeline was also used to examine lung adenocarcinomas and glioblastomas as part of trans Genome Center collaborations, the Tumor Sequencing Project and the nascent Cancer Genome Atlas, respectively. These projects laid the groundwork for the future large-scale efforts at utilizing high-throughput genomic technologies to unravel the cancer genome.
KEYNOTE LECTURE: CHALLENGES OF PEDIATRIC CANCER CLINICAL RESEARCH – PEDIATRIC LIVER TUMORS A MODEL OF CLINICAL RESEARCH AND INTERNATIONAL COOPERATION

Marcio Malogolowkin, MD, Chief, Division Pediatric Hematology-Oncology, UC Davis Medical Center

Hepatoblastoma (HB) and hepatocellular carcinoma (HCC) are the two most common malignant liver tumors in children. They are rare, accounting for only 0.5–1.5% of all childhood malignancies with a total annual incidence of 0.5–1.5 cases per million. This presents a critical barrier to clinical research, which results in the lack of definitive evidence-based data to guide clinical practice. The presentation will discuss the challenges and solutions to overcoming this important clinical need.

IMPACT OF TREATMENT AND INSURANCE ON SOCIOECONOMIC DISPARITIES IN SURVIVAL AFTER ADOLESCENT AND YOUNG ADULT HODGKIN LYMPHOMA: A POPULATION-BASED STUDY

Theresa Keegan, MS, PhD; Division of Hematology and Oncology, UC Davis

Background: Previous studies documented racial/ethnic and socioeconomic disparities in survival after Hodgkin lymphoma (HL) among adolescents and young adults (AYAs), but did not consider the influence of combined-modality treatment and health insurance.

Methods: Data for 9,353 AYA patients aged 15-39 when diagnosed with HL between 1988 and 2011 were obtained from the California Cancer Registry. Using multivariate Cox proportional hazards regression, we examined the impact of socio-demographic characteristics (race/ethnicity, neighborhood socioeconomic status (SES), and health insurance), initial combined-modality treatment, and subsequent cancers on survival.

Results: Over the 24-year study period, we observed improvements in HL-specific survival and differences in survival by race/ethnicity, neighborhood SES and health insurance for a subset of more recently diagnosed patients (2001-2011). In multivariable analyses, HL-specific survival was worse for Blacks than whites with early-stage (Hazard Ratio (HR): 1.68; 95% Confidence Interval (CI): 1.14, 2.49) and late-stage disease (HR: 1.68; 95% CI: 1.17, 2.41) and for Hispanics than whites with late-stage disease (HR: 1.58; 95% CI: 1.22, 2.04). AYAs diagnosed with early-stage disease experienced worse survival if they also resided in lower SES neighborhoods (HR: 2.06; 95% CI: 1.59, 2.68). Furthermore, more recently diagnosed AYAs with public health insurance or who were uninsured experienced greater than a two-fold increased risk of HL mortality.

Conclusion: Our findings identify several subgroups of HL patients at higher risk for HL mortality.

Impact: Identifying and reducing barriers to recommended treatment and surveillance in these AYAs at much higher risk of mortality is essential to ameliorating these survival disparities.

CHILDHOOD CANCER SURVIVORSHIP

Katherine Wells, MS, CPNP, CPON, Division of Pediatric Hematology and Oncology

[No abstract provided at time of print]
My research focuses on the development of cancer-targeted therapies in precursor B cell (preB) acute lymphoblastic leukemia (ALL) and neuroblastoma, the two most common pediatric cancers. We have made significant progress developing a novel antibody-antisense oligonucleotide (ASO) conjugate for preB ALL (Satake et al., patent filed and manuscript submitted). In this conference, I will discuss our progress in the leukemia project.

Despite aggressive treatment, current approaches for preB ALL have significant limitations with a cure rate of only 30% in certain subtypes. In addition, long-term survivors are at risk for late effects that include development of secondary malignancies and organ damage. Therefore, there is a desperate need for more effective and less toxic therapy.

Previously, we demonstrated that the transcription factor MXD3 is a critical regulator of preB ALL cell proliferation. Knockdown of MXD3 expression in preB ALL cells resulted in cell apoptosis (Satake et al., BJH 2014). We hypothesize that targeted delivery of an MXD3 therapeutic to preB ALL cells will increase therapy effectiveness and decrease off target effects and toxicity.

In the current study, we developed a novel conjugate using anti-CD22 antibody (aCD22 Ab), which specifically targets B cell ALL, and an ASO that specifically targets MXD3. Our in vitro studies, using the Reh cell line, indicated successful delivery of the aCD22 Ab-MXD3 ASO conjugate to leukemia cells, which resulted in MXD3 knockdown at the protein level, and leukemia cell apoptosis. The mechanism of action is unknown and will be the subject of further studies. Cytotoxicity of the conjugate was tested on normal blood cells in vitro. As expected, cytotoxicity was observed in normal B cells, but not in CD34 positive hematopoietic stem cells or non-B cells. The combination therapy of the conjugate with vincristine or doxorubicin (conventional preB ALL chemotherapy drugs) showed additive cytotoxic effects in vitro.

We further determined the therapeutic efficacy of the conjugate in pre-clinical xenograft mouse models of preB ALL, using both the Reh cell line as well as a primary leukemia sample (Figure). Age matched female NOD/SCID/IL2Rg-/- mice were randomly assigned to 4 treatment groups: 1) PBS, 2) MXD3 ASO and aCD22 Ab unconjugated, 3) and 4) aCD22 Ab-MXD3 ASO conjugate at two different doses. Following leukemia inoculation, mice were treated twice a week for three weeks. All mice in the control groups died of leukemia at approximately day 21 or day 30 in the Reh or primary leukemia model, respectively. Mice treated with the conjugate, either at low or high dose, had significantly prolonged survival (more than twice) both in the Reh (p<0.0084, n=4/group) and primary leukemia (p=0.0001, n=8/group) models (Log-rank (Mantel-Cox) test). Leukemia-related death was confirmed by necropsy. Harvested leukemia cells were HLA and CD22 positive. During treatment, no toxicities were observed clinically or in blood tests.

In conclusion, we have demonstrated the therapeutic efficacy of the aCD22 Ab-MXD3 ASO conjugate in preB ALL. This is the first study to demonstrate effective direct ASO-conjugated monoclonal aCD22 Ab-mediated delivery for the treatment of leukemia. Future studies will focus on the mechanism of action, development of effective regimens and toxicological profile in vivo, of the conjugate.
LESSONS LEARNED FROM HISTONE MUTATIONS IN PEDIATRIC GLIOMAS

Benjamin Yuen, Dept. Cell. Biol & Human Anatomy

Deregulation of epigenetic pathways or mutations in chromatin components can result in the development of numerous cancers. Recently, recurrent mutations in the histone variant H3.3 were identified in a number of pediatric tumor types. Interestingly, these are some of the first mutations that directly alter the structure of the chromatin, as opposed to mutations in chromatin remodelers, chaperone proteins, or epigenetic modifiers. Point mutations in H3F3A or H3F3B, the only two known genes encoding for H3.3 protein, were found in a majority of pediatric and young adult gliomas and bone or tumors of the cartilage, respectively. This suggests a strong driver role for these changes in oncogenic processes. These substitutions modify critical residues on H3.3 which play a crucial role in gene regulation, in part through interactions with the chromatin modifying Polycomb repressive complex (PRC). A careful balance of PRC activity is needed to appropriately regulate cellular growth and differentiation, and alterations in PRC function have been linked to tumor formation. Work from our laboratory in mouse embryonic stem cells (mESCs) has shown that even changes in the amount of H3.3 present in a cell can affect PRC function. Reductions in H3.3 levels through the inactivation of either H3f3a or H3f3b result in the abnormal expression of genes normally repressed by PRC in mESCs. These changes are accompanied by loss of PRC activity and histone modification within the nucleus. Affected genes are enriched for processes involved in differentiation, and similar to mutations found in pediatric patients, may alter cellular functions leading to oncogenesis. Further characterization of these mutations will allow for a better molecular understanding of these tumors and may catalyze development of additional treatment options to the very limited therapies currently available.

HIV REACTIVATION AND CANCER IMPLICATIONS

Satya Dandekar, PhD, Dept. Medical Microbiology and Immunology, School of Medicine

[No abstract provided at time of print]

GENOMIC LANDSCAPE OF CANINE GLIOBLASTOMA

Kevin Woolard, DVM, PhD, Dept. Pathology, Microbiology and Immunology, School of Veterinary Medicine

Human and canine glioma tumors share many histologic and biologic similarities. Indeed, the domestic dog is the only non-human species that recapitulates every histologic grade of glioma in spontaneous neoplasms. Naturally, this has stimulated much interest in exploring the applicability of the dog as a model for human gliomagenesis. However, there is currently a dearth of knowledge concerning the molecular determinants of canine gliomagenesis. Given the focus on profiling therapeutic options in humans based on molecular subtypes, any meaningful comparison must therefore concentrate on which, if any, subtypes are represented in canine patients. To examine whether canine glioma tumors exhibit similar molecular subtypes as human tumors, we profiled nine canine glioma tumors for copy number alterations and sequenced a subset of commonly mutated genes. We also examined 5 canine glioma stem cell lines in a similar manner. Canine glioma tumors exhibit a similar pattern of large chromosomal amplifications and deletions, although we identified no tumors that share the canonical chromosomal alterations affecting genes involved in human gliomagenesis, namely CDKN2A, EGFR, or PTEN. Instead, canine tumors often exhibited chromosomal amplifications or deletions typically associated with pediatric glioma in humans, including amplification of PDGFRA, PIK3CA, and MET. Additionally, when we examined histone methylation status, we identified that most canine gliomas exhibit a hypomethylated H3K27 residue, in a manner similar to pediatric human glioma tumors. In striking contrast, through serial passage of canine glioma stem cells in orthotopic SCID-mice xenografts,
we are able to recapitulate a genomic landscape remarkably similar to adult human GBM, including loss of CDK2NA and PTEN. Together, these data suggest that the dog may have similarities to both pediatric and adult glioma disease.

ASSOCIATION OF RACCOON POLYOMAVIRUS WITH NEUROGLIAL TUMORS SATYA DANDEKAR, PHD, DEPT. MEDICAL MICROBIOLOGY AND IMMUNOLOGY

Patricia Pesavento, PhD, Dept. Pathology, Microbiology and Immunology, School of Veterinary Medicine

[No abstract provided at time of print]
We discovered that the risk of developing malignant mesothelioma (MM) is transmitted in an autosomal dominant fashion in certain Turkish families in which over 50% of family members developed MM (Reviewed in Carbone M et al., Nature Rev Cancer 2007). In subsequent studies we identified germline mutations in the \textit{BAP1} gene as the cause of MM and uveal melanoma (UM) and other malignancies in some US, European and Australian families (Testa JR. et al., Nature Genetics 2011). Moreover, BAP1 is the most commonly mutated gene is sporadic MM (Nasu M., et al., JTO 2015), a finding that underscores the critical role of BAP1 in MM pathogenesis. BAP1 is a deubiquitylase that associates in the nucleus with multi-protein complexes that regulate key cellular pathways, including transcription, DNA replication and the DNA damage response. All germline \textit{BAP1} mutations identified so far lead to inactive forms of BAP1, lacking deubiquitylating activity or to truncated variants that lack the nuclear localization signal. All carriers of germline \textit{BAP1} mutations studied so far have developed at least one malignancy and many developed multiple cancers (Reviewed in Carbone M., et al., Nature Rev Cancer 2013). Familial MMs in these individuals occur at a median age of 56.3 in either pleura or peritoneum (frequency ratio: 1/1), have a M:F ratio of 0.73:1 and are associated with prolonged survivals of 5-10 or more years; compared to a median age at diagnosis of 72, a 86%:14% pleural/peritoneal ratio; a M:F ratio of 4:1 and a median survival of <1 year in sporadic MM. Thus, MM patients carrying germline \textit{BAP1} mutations benefit from this information. Several families with this cancer syndrome have been described. To identify families with the BAP1 cancer syndrome, we screened patients with family histories of multiple mesotheliomas and melanomas. We identified four families that shared an identical \textit{BAP1} mutation: they lived across the US and did not appear to be related. By combining molecular genetic, family histories taken at the patient’s bedside, and genealogical approaches, we uncovered a BAP1 cancer syndrome kindred of $\sim$ 80,000 descendants with a core of 264 individuals, whose members descend from a couple born in Germany in 1710 (male) - whose ancestors were traced to 1588 in Switzerland and immigrated to Germany in the 17th century - and 1712 (female). The couple immigrated to the USA in the early 18th century. Their descendants spread throughout the country with mutation carriers affected by multiple malignancies. Our data show that once a proband is identified, extended analyses of these kindred using genomic and genealogical studies to identify the most recent common ancestor allows to uncover additional branches of the family that carry \textit{BAP1} mutations. Using this knowledge we have implemented early-detection strategies that led to the identification of early-stage mesotheliomas and melanomas. Our study shows that the application of modern genomic analyses, coupled with “classical” family histories collected by the treating physician, and with genealogical searches, offers a powerful strategy to identify high-risk germline \textit{BAP1} mutation carriers that benefit from genetic counseling and early detection cancer screening.
LUNG MASTER PROTOCOL (LUNG-MAP, S1400): A UNIQUE PUBLIC-PRIVATE PARTNERSHIP FOR CANCER DRUG & BIOMARKER DEVELOPMENT

David R. Gandara, M. Redman, R. S. Herbst, F. R. Hirsch, P. C. Mack, P. N. Lara, Jr, V. A. Papadimitrakopoulou, for UC Davis Comprehensive Cancer Center & The Southwest Oncology Group (SWOG)

In recent years, our understanding of non-small cell lung cancer (NSCLC) has evolved from thinking of this malignancy as a single disease, or a small number of histologic subtypes, to now a multitude of genomically-defined subsets, both in adenocarcinoma and squamous lung cancer. In development of new targeted therapies against these abnormalities, so-called Master Protocols offer a number of advantages over traditional single study designs for drug-biomarker approval, including a common infrastructure, homogeneous patient populations with consistent eligibility across multiple independent sub-studies, and the ability to screen large numbers of patients in rapid fashion. Thus, the Lung-MAP project was designed to facilitate approval of targeted therapy-predictive biomarker combinations in squamous lung cancer, a recognized area of unmet need. Lung-MAP is constructed as a unique public-private partnership engaging the National Cancer Institute (NCI) and its Thoracic Malignancies Steering Committee (TMSC), the Foundation of the NIH (FNIH), the pharmaceutical industry and advocacy groups such as Friends of Cancer Research (FOCR), along with an advisory role by the Federal Drug Administration (FDA). The design is multiple simultaneously running Phase II/III trials, each capable of independently opening and/or closing without affecting the other sub-studies, in which patients eligible for 2nd line therapy for lung SCC have their cancers genomically screened through a next generation sequencing (NGS) platform (Foundation Medicine). Patients are then randomized into one of several sub-studies, each comparing an experimental targeted therapy with standard of care therapy, based on identification of candidate predictive biomarkers associated with each sub-study. At launch, drug targets under study consisted of “match sub-studies” for PI3K, FGFR, CDK 4/6 and HGF, and a non-match sub-study testing PD-L1-directed therapy. Rapid turn-around time of NGS screening results, within 2 weeks, allows real time assignment into the appropriate sub-study. For those patients with cancers that do not “match” into a biomarker-driven sub-study, there is a ‘non-match” sub-study, in which a predictive biomarker is not yet of sufficient validation to utilize it in a drug-biomarker registration strategy. Due to changes in the therapeutic landscape since the launch of Lung-MAP, a number of amendments and modifications have been implemented and new sub-studies have been developed, including study of a PARP inhibitor in cancers demonstrating key abnormalities in homologous DNA repair and a new sub-study comparing PD-L1 inhibition alone versus combined PD-L1/CTL4 inhibition. These and other aspects of Lung MAP will be discussed during this presentation.

SPIDER: SERIAL PATIENT DERIVED XENOGRAFT MODELS TO ELIMINATE CANCER THERAPY RESISTANCE

Thomas J. Semrad, MD, MAS, Jonathan Riess, MD, MS, Edward Kim, MD, PhD, Brian A. Jonas, MD, PhD, Philip C. Mack, PhD, Primo N. Lara, Jr., MD

Background: As a result of surviving and evolving clones, cure of most advanced malignancies with systemic treatment is uncommon. Thus, understanding and overcoming resistance is a major goal of cancer research. Previous work modeling resistance via cell lines resulted in important insights into chemotherapy resistance; however, this system has generally been inefficient in predicting the full spectrum of clinical drug resistance mechanisms. Given the plethora of potential resistance mechanisms, the role of intratumoral heterogeneity in many forms of drug resistance, and the role of tumor microenvironment in adaptive resistance, new models of drug resistance are needed to accurately assess target - drug resistance pairs, to evaluate drug combinations and to develop predictive biomarkers of drug resistance. Patient derived xenograft (PDX) models theoretically overcome many of the limitations of cell lines by maintaining intratumor heterogeneity, a clearer relationship to the disease being studied, a more representative tumor
stroma, and the potential for clinical annotation. Nonetheless, the ability of PDX models to predict sensitivity and resistance to therapeutic intervention requires further validation.

**Methods:** This is a prospective study designed to develop and assess models of resistance to anti-cancer therapy using patient specimens transplanted into NSG mice. For proof of principle, preference is given to tumors with known oncogenic drivers. Enrolled patients undergo a research tumor biopsy for molecular analysis and generation of a PDX prior to treatment. At the time of clinical resistance, a repeat research tumor biopsy is performed for molecular assessment and generation of a second PDX model where feasible. PDXs are established and treated in the CLIA-approved lab at JAX West. The ultimate goal is to establish 1) that treatment of the tumor in the PDX induces the same response as treatment of the native disease and 2) that the molecular changes induced by treatment are correctly modeled by treatment in the PDX system. SPIDER is powered to assess the feasibility this approach and to generate a resource of matched PDX models to evaluate drug resistance in multiple treatment settings.

**Results:** Five patients have been enrolled and four have had pre-treatment biopsies. The driver – treatment pairs included are ROS1 rearrangement – crizotinib, EGFR T790M mutation – rociletinib, and FGFR3-TACC3 fusion – JNJ-42756493. Engraftment of EGFR mutated lung cancer has been inefficient, consistent with literature reports. Pre-treatment model development is ongoing. No resistance biopsies have been collected to date.

**Conclusions:** SPIDER is a platform to validate the PDX platform as a translational model of drug resistance. Enrollment is ongoing.

**Acknowledgements:** This study is supported by the Knapp Family. Dr. Semrad was supported by the National Cancer Institute of the National Institutes of Health under Award Number K12CA138464 during the development of this study.

**STRATEGIES TO ACHIEVE BETTER OUTCOMES FOR PATIENTS WITH UROTHELIAL CARCINOMA**

Chong-xian Pan, Hongyong Zhang, Ai-Hong Ma, Tzu-yin Lin, Clifford Tepper, Susan Airhart, James Keck, Carol Bult, Paramita Ghosh, Paul Henderson, Luis Carvajal-Carmona, Primo Lara, Edson Liu, Ralph de Vere White

Urothelial carcinoma is among the ten most common cancers in the US. The prognosis has not changed significantly over the last three decades. In order to address this issue, the University of California Davis Comprehensive Cancer Center, Lawrence Livermore National Laboratory and The Jackson Laboratory have jointly established a urothelial cancer (UCa) research program. The central theme of this program is to improve patient stratification and treatment of UCa through translational research with the long-term goal of reducing mortality. We hypothesize that the mortality of UCa can be reduced through addressing the unmet medical needs with multi-institutional multidisciplinary translational research using the patient-derived xenograft (PDX) platform. So far, we have established 24 PDXs in immunodeficient NSG mice with annotated clinical information that were developed from uncultured unselected clinical UCa specimens. In general, morphological fidelity was maintained in the PDXs. Whole exome sequencing revealed that PDXs and parental patient cancers shared 92–97% of genetic aberrations, including multiple druggable targets. For drug repurposing, the EGFR/HER2 dual inhibitor lapatinib was effective in PDX BL0440 (progression-free survival or PFS of 25.4 days versus 18.4 days in the control, p=0.007), but not in PDX BL0269 (12 days versus 13 days in the control, p=0.16) although both overexpressed HER2. To screen for effective chemotherapeutic drugs, four of the first six PDXs were sensitive to the cisplatin/gemcitabine combination, and chemoresistance to one drug could be overcome by the other drug. To screen for effective targeted therapy, we evaluated three drugs (lapatinib, ponatinib, and BEZ235) that each matched with the corresponding genetic aberrations in PDX BL0269; but only a PIK3CA inhibitor BEZ235 was effective (p<0.0001). To study the mechanisms of secondary resistance, a fibroblast growth factor receptor 3 inhibitor BGJ398...
pseudonomed PFS of PDX BL0293 from 9.5 days of the control to 18.5 days (p<0.0001), and serial biopsies revealed that the MAPK/ERK and PIK3CA-AKT pathways were activated upon resistance. Inhibition of these pathways significantly prolonged PFS from 12 day for the control to 22 days (p=0.001). To facilitate drug development, a disulfide-crosslinked UCa-specific PLZ4-nanomicelles loaded with paclitaxel were more effective in suppressing PDX growth than free paclitaxel. To begin translation into clinical applications, we compared and found that the response of one patient’s cancer and its derived PDXs were exactly the same to all three lines of therapy in one patient, and the information from the PDX studies were used to guide the decision making for two lines of therapy in that patient, which deviated substantially from the standard of care. In conclusion, the PDX platform allows screening for multiple targeted therapy, chemotherapy, or combinations simultaneously for the most efficacious drugs or combination, serial biopsies during treatment to study drug resistance and for drug development, a task not possibly replicable at the clinical setting.

BLOCKING INDOLAMINE-2,3-DIOXYGENASE REBOUND IMMUNE SUPPRESSION BOOSTS ANTI-TUMOR EFFECTS OF RADIO-IMMUNOTHERAPY IN MURINE MODELS AND SPONTANEOUS CANINE MALIGNANCIES


Previous pre-clinical and clinical studies demonstrate that intratumoral CpG immunotherapy in combination with radiotherapy can act as an in-situ vaccine inducing a robust systemic anti-tumor immune response capable of eradicating systemic disease in some patients. Unfortunately, most patients fail to respond to this therapy. We hypothesized that immunotherapy may paradoxically up-regulate immunosuppressive pathways, a phenomenon we term “rebound immune suppression”, limiting clinical responses. We further hypothesized that the immunosuppressive enzyme indolamine-2,3-dioxygenase (IDO) may be a mechanism of rebound immune suppression and that IDO blockade would improve immunotherapy efficacy. In murine models we observed marked increase in IDO expression within the tumor microenvironment after treatment with local radiotherapy, intratumoral CpG or other immunotherapies. The addition of systemic IDO blockade to local radiotherapy + CpG decreased IDO activity, reduced tumor growth, and reduced immunosuppressive factors, such as regulatory T-cells (Tregs) in the tumor microenvironment. This triple combination induced systemic anti-tumor effects, decreasing metastases and improving survival in a CD8+ T-cell dependent manner. We evaluated this novel triple therapy in a canine clinical trial, since spontaneous canine malignancies closely reflect human cancer. Mirroring our mouse studies, the therapy was well tolerated, reduced local tumor immunosuppression, and induced robust systemic anti-tumor effects. These results suggest IDO up-regulation in the tumor microenvironment maintains immunosuppression after immunotherapy. Systemic IDO blockade may substantially improve treatment efficacy by limiting rebound immunosuppression within the tumor, thereby initiating a local anti-tumor immune response that exerts systemic effects. The efficacy and limited toxicity of this strategy are attractive for clinical translation.

PHASE I EVALUATION OF NANOMICELLE ENCAPSULATED DOXORUBICIN IN DOGS WITH LYMPHOMA

Jenna Burton, DVM, MS, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, Davis, CA, 95616

Nanocarrier formulations of chemotherapy have been investigated as alternatives to antineoplastic drugs with the goal of decreasing normal tissue toxicity while simultaneously improving efficacy. A
novel disulfide cross-linked nano-formulation of doxorubicin has been developed and preclinical studies demonstrate reduced toxicity with this formulation. A phase I study in dogs with lymphoma is on-going to gain additional information regarding the safety and tolerability of nanomicelle-doxorubicin in a large animal model of spontaneously occurring cancer.

Dogs with multicentric lymphoma with no evidence of cardiac dysfunction are eligible for enrollment into this dose-finding clinical trial. Nanomicelle-doxorubicin is administered IV once every three weeks at a starting dose of 20 mg/m²; escalation to 25, 30 and 35 mg/m² is planned pending tolerability. Quality of life assessments are completed by the pet owner and CBC, biochemistry panel and urinalyses are performed weekly to assess toxicity. Plasma samples for PK analysis are collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48 and 96 hours following the first dose. Troponin I is measured pre-treatment and 2 hours post-infusion and a lipid panel performed pre-treatment, 8, 24 and 48 hours after treatment.

Five dogs have been enrolled in the 20 mg/m² dose cohort; one dog developed grade 4 neutropenia at day 7 triggering an expansion of the first dose cohort. Other adverse events have been mild and self-limiting to date. Three dogs with treatment naïve B-cell lymphoma experienced a partial response that was durable for 42 to 105 days; the other two dogs developed progressive disease on day 4 and day 21.

These preliminary data suggest that nanomicelle-doxorubicin is safe and well tolerated in dogs with lymphoma and with evidence of efficacy noted in the first dose cohort.

EXPANDING OUR SENSES: NOVEL DIAGNOSTIC TECHNOLOGIES FROM GERMAN LASERS TO GERMAN SHEPHERDS

Gregory Farwell, MD, FACS, Dept. Otolaryngology

[No abstract provided at time of print]
ABSTRACTS OF ORAL PRESENTATIONS (FRIDAY)
SESSION III – UC DAVIS BIOMEDICAL IMAGING PROGRAM
Chair: Julie Sutcliffe, PhD

MOLECULAR IMAGING AT UC DAVIS

Julie Sutcliffe PhD, Department of Internal Medicine and Biomedical Engineering

Molecular imaging is a powerful non-invasive tool that monitors and records the spatiotemporal distribution of molecular or cellular processes for diagnostic or therapeutic applications. The impact of Molecular Imaging on oncology encompasses all aspects of clinical management including early detection, guiding the preclinical development of targeted therapeutics and biomarkers, assisting staging of disease and monitoring response to therapeutics. Utilization of Molecular Imaging can significantly decrease the costs incurred with the development of new therapies by allowing accurate patient treatment stratification and allowing the non-invasive serial assessment of the biological response to treatment in vivo. UC Davis has made significant investments in the infrastructure necessary to build a successful Translational Molecular Imaging Program. Dr. Sutcliffe will describe some of these unique imaging resources including CMGI, CNPRC and the new GMP radiochemistry facility. She will highlight some of the current applications of molecular imaging and describe future opportunities for oncology applications.

KEYNOTE LECTURE: THE EXPLORER TOTAL BODY PET SCANNER PROGRAM AT UC DAVIS

Terry Jones, DSc, Visiting Professor, UC Davis; Co-Director PET Research Advisory Company

UC Davis has been awarded a major NIH grant to build the World’s first total body PET scanner and to demonstrate that the ability to simultaneously record the whole body’s distribution of a radiolabelled biomarker and the corresponding high sensitivity, offers a significant step change for the applications of PET based molecular imaging in clinical research and health care.

An overview of the EXPLORER program will be presented including the projected applications of the scanner to effect high sensitivity detection of multi-systems pathology, whole body kinetics, “systems” body interactions, and ultra-low radiation absorbed dose studies.

Examples for applications in cancer will be discussed. They are seen to lie in the: i) detection of low density micro-metastatic disease, ii) support for drug development and targeting, by recording of pharmacokinetics within the primary tumour, metastatic deposits and normal tissues, iii) support for the development of new cancer imaging bio-markers and iv) through kinetic studies, measurement of functional distribution spaces within solid tumours.

QUANTITATIVE KINETIC MODELING APPROACHES FOR HUMAN MOLECULAR IMAGING STUDIES

Guobao Wang, PhD, Dept. Biomedical Engineering

Dynamic PET imaging is able to monitor spatial and temporal distributions of a radiotracer in vivo. With tracer kinetic modeling, mathematical models can be used to interpret dynamic data and quantify the molecular process of a specific radiotracer in the body. The combination of dynamic imaging and kinetic modeling has emerged as a powerful quantitative tool in human molecular imaging studies. This quantitative technique, however, has been historically limited to regional quantification due to image noise, less reliable to characterize small tumors and intratumoral heterogeneity. We have developed an innovative kernel-based dynamic PET imaging method and
demonstrated substantial improvements on image quality on clinical PET scanners. Robust voxel-wise kinetic quantification has been enabled to generate parametric images of biologically important kinetic parameters (e.g. glucose metabolism, binding potential). This development has opened up new opportunities for discovering the portraits of cancer heterogeneity using in vivo molecular imaging.

MICROFLUIDIC CULTURE SYSTEMS USED TO STUDY PARACRINE AND AUTOCRINE SIGNALS IN THE CANCER MICROENVIRONMENT

Alex Revzin, PhD, Dept. Biomedical Engineering

This presentation will describe our recent efforts to develop microfluidic devices for cultivation of a number of cell types, including cancer cells. These microfluidic devices offer interesting advantages compared to standard cultures. Because volumes inside microfluidic devices are small, cell-secreted signals accumulate, reach threshold concentrations and have profound effects on cell phenotype – something that is difficult to replicate in standard (large volume) cultures. In collaboration with scientists from Genentech we wanted to understand the role of FGF-2 in mediating acquired drug resistance to vemurafenib in BRAF mutant melanoma cells. We hypothesized that FGF-2 was produced by a subpopulation of resistant cells in the cancer microenvironment, conferring resistance to neighboring sensitive cells. However, we were unable to make this connection using traditional approaches – conditioned media and transwell co-cultures.

An alternative strategy explored by us involved a microfluidic system comprised of two compartments separated by a 100 micrometer wide hydrogel barrier. The barrier prevented resorting of resistant and sensitive cancer cells cultured in the adjacent compartments but allowed for paracrine signals to diffuse freely. In this co-culture system, sensitive melanoma cells became refractive to vemurafenib when cultured next to resistant cells. Furthermore, this microfluidic co-culture device could be further modified by incorporation of FGF-2 ligand trap into the hydrogel barrier separating resistant and sensitive melanoma cells. With FGF-2 ligand trap in place, resistance was broken, sensitive cells became responsive to vemurafenib and were no longer affected by the neighboring resistant cells. Broadly speaking, microfluidic system may better recapitulate high local concentrations of secreted signals observed in vivo than traditional large volume cultures. Microfluidic systems may be designed to eliminate or knock-down specific paracrine signals of interest from the cancer microenvironment to establish cause-effect relationships. We also envision utilizing microfluidic devices for maintaining difficult to culture cells, such as primary cancers or patient derived xenografts.

A THERANOSTIC NANOPORPHYRIN PLATFORM

Yuanpei Li, Tzu-yin Lin, Sebastian Wachsmann-Hogiu, Simon R. Cherry, Douglas J. Rowland, Chong-xian Pan, Kit S. Lam

We have developed a highly innovative theranostic nanoporphyrin (NP) platform for the integration of a broad range of imaging and therapeutic functions, including magnetic resonance imaging (MRI), positron emission tomography (PET), fluorescence optical tomography (FOT), phototherapy and targeted drug delivery. NPs exhibit architecture-dependent fluorescence- and magnetic resonance- properties, which could significantly increase the sensitivity of optical imaging and MRI for tumor detection. Furthermore, we have demonstrated that these NPs not only target early primary tumors, but also efficiently detect very small spontaneous micro-metastasis. The superior imaging capability of NPs can be further utilized to monitor the real-time in vivo delivery of NPs and assess their therapeutic efficacy non-invasively. The NPs represent a new generation of smart multifunctional nanoparticles for convenient integration of a broad range of “intelligent” imaging and therapeutic functions that simultaneously addresses the complex requirements of multimodal imaging, photo-therapy and drug delivery by a simple approach.
This presentation overviews fluorescence lifetime spectroscopy and imaging techniques for label-free *in vivo* characterization of biological tissues. Emphasis is placed on recently developed devices and methods enabling real-time delineation and diagnosis of tumors during clinical interventions. I will present studies conducted in animal models and human patients demonstrating the ability of these techniques to provide rapid in-situ evaluation of tissue biochemistry and their potential to guide surgical procedures. Current results demonstrate that intrinsic fluorescence can provide useful contrast for intraoperative delineation of brain tumors and head and neck tumors. Finally, I will present results from the first-in-human study that shows the potential of a multispectral fluorescence lifetime method for image-guided augmented reality in trans-oral robotic surgery (TORS).
KEYNOTE LECTURE: PROMISES AND PITFALLS OF CANCER GENOMICS

John McPherson, PhD, UC Davis Comprehensive Cancer Center as Deputy Director and Associate Director for Basic Sciences (Department of Biochemistry and Molecular Medicine)

The human genome reference sequence was “finished” more than 10 years ago and to many heralded the post-genomic era. Driven largely by rapid advances in sequencing technologies, we have continued to improve the reference genome, capture sequence diversity and analyze thousands of healthy and disease associated genomes. The complexity of the human genome is now only being appreciated, no more so than in cancer. We are truly just scratching the surface on genome discovery and applications to improve human health.

A POPULATION-BASED STUDY OF HIGHLY PENETRANT GENES FINDS THAT ONE IN FOUR YOUNG HISPANIC WOMEN WITH BREAST CANCER CARRY BRCA1/2 OR PALB2 MUTATIONS

Anna Marie de Asis Tuazon1*, Mabel Bohorquez2*, Carolina Ramirez2, Paul Lott1, Ana Estrada2, Angel Criollo2, Rodrigo Prieto2, Cathy Wang1, Carolina Sanabria3, Martha Serrano3, Raul Murillo3, Justo Olaya4, Gilbert Mateus2, Post-Columbian Study of Environmental and Heritable Causes of Breast Cancer (COLUMBUS) Consortium5, Latin American Cancer Genetics (LaFamilia) Consortium6, Magdalena Echeverry2, Luis G. Carvajal Carmona1,2,5

1 Genome Center and Department of Biochemistry and Molecular Medicine, School of Medicine
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5 The full list of COLUMBUS and LaFamilia Consortium members is presented in the acknowledgements
6 Fundación de Genómica y Genética Molecular, Colombia

Breast cancer is the leading cause of cancer incidence and death among Hispanic women, who are diagnosed with breast cancer at much later stages and more likely to die after diagnosis compared to non-Hispanic whites. Investigating the breast cancer etiology, including its genetic basis, has direct implications in designing comprehensive, cost-effective screening for clinical intervention and management of the disease. In this study, we screened 663 unselected breast cancer cases from Colombia using a hierarchical approach of genotyping known Hispanic mutations followed by targeted next generation sequencing of the BRCA1, BRCA2 and PALB2 genes. We identified 66 pathogenic mutation carriers (10%), 89.4% of which were recurrent, founder mutations (n=59/66). This included the profound founder mutation BRCA1 3450del4, which was found in 32 cases and accounted for 5% of all unselected cases. Identity-by-descent analysis of the BRCA1 3450del4 founder mutation in >60 families from Spain, Portugal, Africa, Chile, and Colombia supported a single origin of the mutation in the Iberian Peninsula. Our study was the first to identify pathogenic mutations in PALB2 in a Hispanic population. We found a high prevalence (0.9%) of PALB2 mutations in our unselected cohort, including the novel founder mutation PALB2 c.2288delTTCA, which was found in four cases. This suggests that PALB2 plays an important role in breast cancer susceptibility among Hispanics. Remarkably, we report one of the highest prevalence of BRCA1/2 mutations in any unselected breast cancer study, with 9% of the cohort carrying a mutation. Irrespective of a family history of cancer, roughly 1 in 4 women diagnosed with breast cancer by age 40 years carried a BRCA1/2 or PALB2 mutation in our study. These findings support the premise that population-based genetic screening among young Hispanic women would identify many carriers not typically evaluated by clinic, family-based criteria, ultimately leading to earlier diagnoses and improved outcomes.
MOLECULAR ONCOLOGY TUMOR BOARD

Karen Kelly, MD, Professor of Medicine, Division of Hematology Oncology

In this era of precision medicine, molecular profiling of tumors is routinely incorporated into standard clinical practice. However, most clinicians do not have the genomics expertise that is frequently required to interpret these results. The UC Davis Comprehensive Cancer Center, in partnership with Foundation Medicine, has established a monthly Molecular Oncology Tumor Board to assist clinicians in deciphering complex molecular profiles and offer therapeutic guidance. The tumor board is comprised of a multidisciplinary team of clinicians, pathologists, translational scientists, geneticists and bioinformatics specialists who present and discuss patient cases. This presentation will give an example of a tumor board case and discuss the value it brings to clinical practice and clinical research.

CLINICAL TRIAL USING BIOENGINEERED STEM CELLS TO TREAT HIV PATIENTS SUFFERING FROM LYMPHOMA

Mehrdad Abedi MD, Professor, Division of Hematology Oncology, UC Davis School of Medicine

Survival in patients infected with the Human Immunodeficiency Virus (HIV) has improved dramatically with the advent of Antiretroviral Therapy (ART). However, neither a cure for HIV nor an efficacious vaccine exist, patients need to take ART with high compliance for the rest of their lives. Lack of immunological response, issues with non-compliance or drug resistance, side effects of ART, persistently higher incidence of HIV related malignancies and a poorly understood chronic inflammatory status associated with different chronic illnesses are just a few of the complications continuing to diminish quality of life in HIV patients.

Hematopoietic stem cell (HSC) gene therapy for HIV may offer an alternative one-time treatment, with the possibility of controlling reservoirs of HIV responsible for persistence of the disease despite ART. We have developed novel anti-HIV genes and a preclinical in vivo HIV model for testing these genes, and are now planning a human stem cell gene therapy trial. Our novel anti-HIV therapeutic candidate, autologous HSCs transduced with a triple combination of anti-HIV genes transferred by a single lentiviral vector is aimed at blocking HIV infection at different stages of the HIV life cycle. This approach provided strong pre-integration inhibition of HIV-1 infection, decreased the generation of viral escape mutants and prevented the integration of multiple, including resistant, strains of HIV in various cell types in vitro. In vivo safety/efficacy studies in a humanized mouse model displayed excellent results including a selective survival advantage of anti-HIV gene modified cells and maintenance of normal human CD4+ cell levels.

We are using a novel method of transduction to increase transduction efficiency into HSCs to clinically useful levels. Furthermore, we use a selectable surface marker for purification of transduced cells and transplant only anti-HIV gene expressing cells. By doing so, we target relapsed HIV related B cell lymphoma patients that require transplant as a part of their standard of care providing an ethically acceptable setting to test the safety and efficacy. Newly arising HIV-resistant immune cells will arise, survive and expand in the face of a viral load, developing an HIV resistant immune system to control HIV for the life of the patient. By using a highly effective combinatorial anti-HIV gene therapy approach, developing a novel and significantly improved transduction process, revising transplant procedures to transduce HSCs before freezing and, most importantly, selecting and transplanting only the HIV resistant transduced HSCs, we expect to replace the patient’s immune system with HIV resistant cells, thus driving down the viral load in the absence of ART.
POSTER PRESENTATIONS

Courtyard by Marriott Hotel
4422 Y Street, Sacramento

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Thursday poster session: 11:55 am – 1:45 pm
Posters can be put up from 7:30 am
Posters must be taken down by 2:00 pm

Friday poster session: 11:25 am – 1:15 pm
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Posters must be taken down by 2:00 pm
1. Regulation of the T-Box Transcription Factor TBX3 by the Tumor Suppressor MicroRNA-206 in Breast Cancer
   Sumaira Amir, Catalina Simion, Maxine Umeh, Sheryl Krig, Tyler Moss, Kermit L. Carraway III and Colleen Sweeney

2. Cancer Metastasis Aging by Carbon 14 Dating
   Bruce A. Buchholz, Laurel Beckett, Kenneth W. Turteltaub, G. Steven Bova

3. Discovery of Ligands for the Development of Exosome Diagnostics
   Randy P. Carney, Sidhartha Hazari, Alisha Knudson, and Kit S. Lam

4. Characterizing HER2 Gene Variation to Address Racial Disparities in Breast Cancer Mortality
   Wei He, Matthew Saldana, Tiffany Scharadin, Kermit Carraway, Paul Henderson, Matthew A. Coleman

5. Sociodemographic Disparities in Survival for Adolescents and Young Adults with Cancer Differ by Health Insurance Status, a Population Based-Study in California, 2001-2011
   Mindy C. DeRouen, Helen M. Parsons, Erin E. Kent, Brad H. Pollock, Theresa H. M. Keegan

6. A Study of the Effect of p53 Mutation on Radiation Resistance in Prostate Cancer
   Angshumala Goswami, Ruth L Vinall, Clifford G. Tepper, Ralph W. deVere White, Paramita M Ghosh

7. Activation of Photodynamic Therapy in vitro with Cerenkov Luminescence Generated from Yttrium-90
   Brad A. Hartl, Henry Hirschberg, Laura Marcu, Simon R. Cherry

8. Label-Free Fluorescence Lifetime Detection of Radiation-Induced Brain Necrosis in Live Rats
   Brad Hartl, Htet Su Wai Ma, Katherine Hansen, Anthony Valenzuela, Melanie Klich, Julian Perks, Kyoungmi Kim, Michael Kent, Fredric Gorin, Ruben Fragoso, Laura Marcu

9. Demonstration of KRAS Dimerization in Nanolipoprotein Particles
   Denise J. Trans, Ruiwu Liu, Stephan Gysin, Tiffany Scharadin, Kit S. Lam, Matthew A. Coleman, Frank McCormick and Paul T. Henderson

10. Targeting Noncanonical Wnt-Ror Signaling in Cancer Metastasis
    Edith Karuna, Michael Schlein, Kit Lam and Henry Ho

11. In vivo Analysis of EGFR Family Signaling as a Bypass Mechanism in Prostate Cancer
    Maitreyee K. Jathal, Thomas M. Steele, Salma Siddiqui, Benjamin A. Mooso, Leandro S. D’Abronzo, Christiana Drake, Young E. Whang and Paramita M. Ghosh

12. A Personal Health Network for Chemotherapy Care Coordination: Evaluation of Usability Among Patients
    Katherine K. Kim, Janice F. Bell, Richard Bold, Andra Davis, Victoria Ngo, Sarah C. Reed, Jill G. Joseph

13. Clinical Predictors of Survival in Small Cell Lung Cancer (SCLC) Patients < 50 Years of Age: Results from the California Cancer Registry
    Joshua D. Lara, Ann Brunson, Jonathan W. Riess, Karen Kelly, Primo N. Lara Jr., and David R. Gandara
14. Determinants of Survival in Adolescents and Young Adults with Urothelial Bladder Cancer: Results from the California Cancer Registry
Joshua Lara, Ann Brunson, Theresa Keegan, Chong-Xian Pan, Stanley Yap, Marcio Malogolowkin and Ralph de Vere White

15. SWOG 0709: Randomized Phase II Trial of Erlotinib vs. Erlotinib Plus Carboplatin/Paclitaxel in Patients with Advanced Non-Small Cell Lung Cancer and Impaired Performance Status as Selected by a Serum Proteomics assay

16. Our Feathered Friends: Pigeons (Columba Livia) as Trainable Observers of Pathology and Radiology Breast Cancer Images
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THURSDAY POSTER PRESENTATIONS (ABSTRACTS)

<<1>> REGULATION OF THE T-BOX TRANSCRIPTION FACTOR TBX3 BY THE TUMOR SUPPRESSOR MICRORNA-206 IN BREAST CANCER

Sumaira Amir1, Catalina Simion1, Maxine Umeh1, Sheryl Krig1, Tyler Moss2, Kermit L. Carraway III1 and Colleen Sweeney1

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Tbx3 is a transcriptional repressor and regulator of mRNA splicing. Germ line mutations in Tbx3 lead to Ulnar-Mammary syndrome, which is notable for severe breast hypoplasia among other developmental abnormalities. Tbx3 is also required for the development of the mouse mammary gland and is essential for the generation of the hormone sensing lineage. Tbx3 has oncogenic activity and is over-expressed in human breast cancer, where it has been implicated in proliferation, migration and regulation of the cancer stem cell population. Mechanisms which regulate Tbx3 expression in cancer have not been extensively explored. In this study, we examine the regulation of Tbx3 by the tumor suppressor microRNA, miR-206. We demonstrate that Tbx3 is directly repressed by miR-206 and that this repression of Tbx3 is necessary for miR-206 to inhibit breast tumor cell proliferation and invasion and decrease the cancer stem cell population. Moreover, Tbx3 and miR-206 expression are inversely correlated in human breast cancer. These studies uncover a novel mechanism of Tbx3 regulation and identify a new target of the tumor suppressor miR-206.

<<2>> CANCER METASTASIS AGING BY CARBON 14 DATING

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Background. Despite advances in the treatment of some primary cancers since the early 1970s, metastatic cancer remains lethal in the majority of cases. Methods to estimate tumor metastatic “trajectory” in individual patients could improve understanding of the biology of metastasis, and improve selection of appropriate therapy. Recent advances have shown that high-depth DNA sequence information can be used to estimate the relative genetic origins of metastatic subclones within patients, and to estimate whether separate regions of primary cancers in the same patient have common genetic origins. In order to determine if it could be used to establish an independent line of evidence important to understand metastatic tumor physiology in relation to tumor genetic evolution, we used 14C DNA birth dating of cells to measure the average cellular ages of primary prostate tumors, metastatic lesions, and healthy tissue in three subjects.

Methods. Primary prostate tumors, metastatic lesions and normal tissue were collected at autopsy. Tissues were digested using proteinase K and DNA was isolated using phenol-chloroform extraction. F14C levels in DNA were measured by accelerator mass spectrometry to determine the average age that was correlated among subjects.

Results. 12 metastatic lesions, 3 primary prostate cancers, and 4 normal tissue controls were analyzed from 3 subjects. DNA dating followed relatively closely in all three cases the hypothesized sequence, with normal followed by prostate cancer, then lymph node and other metastases (p=0.055). The bone metastases tended to have the youngest DNA.

Conclusions. The average age of cancer cells is significantly younger than normal tissue. Rapidly growing cells such as metastatic lesions possess the youngest DNA.

This work was performed in part under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.
DISCOVERY OF LIGANDS FOR THE DEVELOPMENT OF EXOSOME DIAGNOSTICS

Randy P. Carney, Sidhartha Hazari, Alisha Knudson, and Kit S. Lam
Department of Biochemistry and Molecular Medicine, UC Davis

There is an urgent need in clinical sciences for new non-invasive technologies capable of rapidly diagnosing cancers in their early-stage and according to subtype. Fortuitously, all cells dynamically excrete into circulation nano-sized packages called exosomes for normal cell-to-cell communication. It was recently discovered that cancer cells hijack exosomal communication pathways by tweaking their contents for means of immune system suppression and metastasis. Exosomes are composed of molecular contents spanning the range of lipids, proteins, genes (especially miRNAs), and metabolites, and thus hold great potential for cancer diagnostics. Yet distinguishing tumor-associated exosomes from healthy ones is not currently possible. Hence, the ability to separate circulating exosomes into subpopulations according to their tissue of origin or state of disease could provide a powerful approach for clinical diagnosis and prognosis of cancers. Recently we have identified several novel exosome-binding ligands via a combinatorial-based screening method, which could be used to "sense" tumor-associated exosomes in biofluids like blood or urine. Our peptide-based ligands are capable of binding exosomes derived from solid tumor ovarian cancer cells and lymphoid tumor leukemia cells, respectively, but show little affinity to other types of normal cell-derived exosomes. We believe a ligand-based targeting approach has the potential to transform both the understanding of compositional differences amongst circulating exosomes and also the way cancer is diagnosed. We plan to engineer diagnostic platforms capable of fingerprinting exosome subpopulations through their unique binding signatures to combinations of capturing ligands.

CHARACTERIZING HER2 GENE VARIATION TO ADDRESS RACIAL DISPARITIES IN BREAST CANCER MORTALITY

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Abstract: African-American women have a much higher rate of breast cancer mortality than Caucasian women. Notably, African-American women are also found to be at greater risk for more aggressive forms of breast cancer known as triple negative. Recently, a single nucleotide polymorphism (SNP) of HER2, W452C, which occurs predominantly in African-American women (about 10% frequency), was reported significantly correlated with breast cancer. This study reported that tumors from patients harboring W452C do not amplify the erbb2 (HER2) gene or overexpress the protein, suggesting that this variant may contribute to breast cancer development through a novel mechanism. To study the structural and functional differences associated with W452C, first we looked at over-expression of HER2 harboring W452C mutation in cells, which resulted in increased disulfide dimer formation, likely caused by the extra cysteine in extracellular domain. Expression of HER2-W452C also increased basal ATK signaling, which could lead to enhanced tumorigenecity. To address the biochemical role of the W452C SNP in breast cancer we applied a cell-free in vitro reconstitution system that uses nanolipoprotein particles (NLPs) to solubilize and support functional membrane proteins. Cell-free produced wild type HER2 and W452C were tested for tyrosine phosphorylation as well as specific binding to therapeutic anti-HER2 monoclonal antibodies trastuzumab and pertuzumab. Our results showed comparable tyrosine phosphorylation levels for both wild type and W452C HER2, suggesting that the variant itself might not alone be a driver of cancer. We also observed a decreased binding affinity of
trastuzumab for W452C compared to wild type HER2, indicating that W452-positive patients might not respond to trastuzumab treatment. On the other hand, W452C had a higher affinity for pertuzumab, which may be a better alternative treatment. Overall, our studies suggest that the W452C variant may account for a cancer cell phenotype through a distinct signal pathway. Breast tumors bearing this HER2 variant may be differentially sensitive to clinically pertinent therapeutic agents. Further characterization of this variant will be important for the development of more effective and precise therapeutic intervention treatment regime. This in turn could lead to better diagnostic decisions to identify the W452C variant and use of targeted measures that better help address racial disparity problems in breast cancer mortality.

SOCIODEMOGRAPHIC DISPARITIES IN SURVIVAL FOR ADOLESCENTS AND YOUNG ADULTS WITH CANCER DIFFER BY HEALTH INSURANCE STATUS, A POPULATION BASED-STUDY IN CALIFORNIA, 2001-2011

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Background: This study aimed to investigate the independent and joint associations of sociodemographic factors—race/ethnicity, neighborhood socioeconomic status (SES), and insurance type at diagnosis—with survival for AYAs with invasive cancer and for those with the most common AYA cancers.

Methods: Data on 80,855 eligible AYAs with invasive cancer diagnosed in California during 2001-2011 were obtained from the California Cancer Registry. We used multivariable stratified Cox proportional hazards regression to report hazard ratios (HRs) and 95% confidence intervals (CIs) for overall survival for AYAs with all invasive cancers, highlighting the modifying effects of age and insurance status on race/ethnicity and neighborhood SES, and for twelve of the most common AYA cancers.

Results: AYA age group and insurance type at diagnosis modified associations of non-White race/ethnicity and lower neighborhood SES with shorter overall survival. Associations of non-White race/ethnicity with survival were more pronounced for AYAs with private/military insurance and for younger AYAs. While neighborhood SES disparities among AYAs with public insurance were limited, there were step-wise neighborhood SES disparities among those with private/military insurance that worsened with increasing age. Associations of race/ethnicity and neighborhood SES differed by cancer site, but associations of no or public insurance with lower survival were observed for 11 of 12 sites examined (HRs from 1.16 (95% CI 1.04-1.29) for leukemia to 2.61 (95% CI 2.13-3.20) for melanoma).

Conclusions: Lacking or having public insurance was consistently associated with lower survival for AYAs of all ages and with the most common types of cancer, while associations of race/ethnicity and neighborhood SES with survival persisted for some age groups, for those with private insurance, and for some cancer sites. Our findings highlight the negative effects of lacking or having public health insurance on survival, but also indicate that among AYAs with private health insurance, those of Black or Hispanic race/ethnicity or who reside in lower SES neighborhoods suffer from persistent survival disparities, and further research is needed to identify the factors mediating these disparities.
A STUDY OF THE EFFECT OF P53 MUTATION ON RADIATION RESISTANCE IN PROSTATE CANCER

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Background: p53 is a major tumor suppressor whose function is pivotal for protection against prostate cancer (CaP). Ionizing radiation (IR), a standard-of-care treatment for localized CaP, causes substantial DNA damage triggering p53 activation and stabilization. A TP53 hotspot mutant, R273H, alters the ability of p53 to transcribe target genes and this may contribute to patient resistance to radiation therapy. The goal of this project is to identify the downstream effectors of p53 mutation that mediate radiation resistance in prostate cancer cells.

Methods: Androgen-dependent CaP cells, LNCaP, were stably transfected with the TP53 R273H mutant allele (LNCaP-R273H) and an empty vector control. RNA was extracted from cells 6 hours after exposure to 10Gy radiation. Expression of mRNA was assessed by microarray analysis.

Result: Out of all the genes analyzed, 3425 genes were selected as having statistically significant differential expression based on hypothesis testing. Among these 3425 genes, 951 in LNCaP and 1107 in R273H showed differential regulation when irradiated, based on a 1.5 fold change cutoff. 695 were similarly altered in both. 256 exhibited differential regulation in LNCaP cells but not in R273H cells. Comparison of the two cell lines showed that basal expression of 1,471 genes exhibited differential expression consequent to R273H expression (i.e., at 0Gy), but 585 were differentially expressed in response to IR at 10Gy. 46 genes were differentially regulated by IR due to R273H mutation. Of the 46, 20 were altered in opposite directions by radiation and mutation, and were thought to be candidates for mediating radiosensitivity in LNCaP but are prevented from doing that in R273H. mRNA sequence data was available for 15 of these genes, of which 10 were also differentially regulated (R273H vs LNCaP) (EPAS1, CSDA, LONRF2, ZNF415, RLN1, RND3, PHLDA3, LAMB1, ELOVL6, CKAP2). qPCR was done to validate the results and identify interesting candidates for further analysis.

Conclusion: The above analysis identifies candidates that potentially regulate radiation resistance in CaP. Further studies are necessary to determine whether the mRNA identified is also regulated by androgen receptor.

ACTIVATION OF PHOTODYNAMIC THERAPY IN VITRO WITH CERENKOV LUMINESCENCE GENERATED FROM YTTRIUM-90

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Translation of photodynamic therapy to the clinical setting has primarily been limited to easily accessible and/or superficial diseases where traditional light delivery can be performed noninvasively. Cerenkov luminescence, as generated from medically relevant radionuclides, has been suggested as a means to deliver light to deeper tissues noninvasively in order to overcome this depth limitation. We report on the use of Cerenkov luminescence generated from Yttrium-90 as a means to active the photodynamic therapy process in monolayer tumor cell cultures. The current study investigates the utility of Cerenkov luminescence for activating both the clinically relevant aminolevulinic acid at 1.0 mM and also the more efficient photosensitizer TPPS2a at 1.2 µM. Cells were incubated with aminolevulinic acid for 6 hours prior to radionuclide addition, as well as additional daily treatments for three days. TPPS2a was delivered as a single treatment with an 18 hour incubation time before radionuclide addition. Experiments were completed for both C6
glioma cells and MDA-MB-231 breast tumor cells. Although aminolevulinic acid proved ineffective for generating a therapeutic effect at any activity for either cell line, TPPS2a produced at least a 20% therapeutic effect at activities ranging from 6 to 60 µCi/well for the C6 cell line. Current results demonstrate that it may be possible to generate a therapeutic effect in vivo using Cerenkov luminescence to activate the photodynamic therapy process with clinically relevant photosensitizers.

**LABEL-FREE FLUORESCENCE LIFETIME DETECTION OF RADIATION-INDUCED BRAIN NECROSIS IN LIVE RATS**

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Differentiating recurrent tumor from radiation induced necrosis in the brain remains a significant challenge to the neurological surgeon. Traditional MRI scans are not able to reliably discriminate the two tissue types, making biopsy location selection and surgical management difficult. Label-free fluorescence lifetime techniques have previously been shown to be able to delineate human brain tumor from healthy tissues. Thus, fluorescence lifetime techniques represent a potential means to delineate the two tissues in real-time during surgery. This study aims to characterize the endogenous fluorescence lifetime signatures from radiation induced brain necrosis in a tumor-free rat model. Fischer rats received a single fraction of 60 Gy of radiation to the right hemisphere using a linear accelerator. Animals underwent a terminal live surgery either two weeks before the onset of necrosis or approximately 3-4 weeks after gross necrosis had developed, as determined by MRI. During surgery, healthy and necrotic brain tissue was measured with a fiber optic needle connected to a multispectral fluorescence lifetime system. Preliminary results show that necrotic tissue has a 25% increase in lifetime and decrease in intensity relative to healthy tissue. No significant changes or shifts in the spectral intensity were observed in the necrotic regions, suggesting that the primary contrast mechanism lies within the subpopulation shifts of nicotinamide adenine dinucleotide, the primary endogenous fluorophore of healthy brain tissue. These results show for the first time that radiation induced brain necrosis tissue contains significantly different metabolic signatures that are detectable with label-free fluorescence lifetime techniques.

**DEMONSTRATION OF KRAS DIMERIZATION IN NANOLIPOPROTEIN PARTICLES**

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Ras is an oncogenic protein that is mutated in approximately 30% of cancers. KRAS is the isoform found most frequently mutated in cancers. Cancer promoting mutations within the Ras GTP-binding domain prevent Ras from hydrolyzing GTP, keeping it in an active conformation which stimulates cell-signaling pathways that ultimately result in cellular proliferation and survival. Though Ras is widely considered to be monomeric, recent studies suggest that Ras may dimerize at the cell membrane, and that the dimerized form of the protein elicits enhanced signaling.
Understanding the mechanisms underlying Ras dimerization will aid in the development of therapeutic strategies and agents that target the Ras protein. Model membrane systems, such as liposomes or supported lipid bilayers, are powerful tools for studying membrane proteins outside of cellular environments for various biophysical or biochemical analyses. Nanolipoprotein particles (NLPs), or nanodiscs, are one such bilayer membrane model that has been used to study many membrane proteins including G-protein coupled receptors, ion channels, and receptor tyrosine kinases. This project proposes to use NLPs to study KRAS self-association on membrane surfaces to 1) establish NLPs as a suitable model to study Ras proteins, and 2) to elucidate the potential role of KRAS dimerization on its function. This will be done first by incorporating purified, post-translationally modified (farnesylated) KRAS proteins produced in insect cells into NLPs and confirming the activity of the GTPase. Next, fluorescence-based assays, including fluorescence resonance energy transfer (FRET) using novel fluorescently-labeled GTP analogs, will be used to measure the distance between KRAS proteins within a dimer or to identify the oligomeric state of KRAS proteins on NLP surfaces. The implications of dimerization in normal activity as well as activating mutations of KRAS are important for understanding both KRAS regulation in cell signaling pathways and possible areas to target Ras for future therapeutics.

**TARGETING NONCANONICAL WNT-ROR SIGNALING IN CANCER METASTASIS**

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The Wnt family of secreted glycoproteins controls diverse developmental and oncogenic processes. The canonical mechanisms by which Wnts signal via the transcription factor beta-catenin to control cell differentiation, proliferation and cancer induction have been extensively characterized. However, a subset of Wnts, such as Wnt5a, can function independently of beta-catenin to control morphogenetic cell behaviors, such as cell polarization, adhesion and migration. This “noncanonical” mode of Wnt signaling has recently emerged as a major player in cancer metastasis, yet its underlying molecular mechanisms remain poorly defined. We have integrated mouse genetics and proteome-wide mass spectrometry analysis to delineate a novel Wnt5a signaling pathway involving the Ror family of receptor tyrosine kinases, the scaffolding protein Dvl, and the kinesin-like protein Kif26b. Mechanistically, the Wnt5a-Ror-Dvl axis modulates the stability of Kif26b, which in turn controls cell migration activity. In addition, Ror receptors are promising biomarkers and validated drug targets for metastatic cancers. We have therefore sought to identify small-molecule compounds that can modulate the Wnt5a-Ror axis through interaction with Ror receptors. To this end, we have screened a One-Bead-One-Compound (OBOC) combinatorial peptide library and identified a number of compounds exhibiting specific binding affinity toward Ror receptors. Further characterization of these compounds is currently underway. In summary, our work has defined a novel molecular framework of the noncanonical Wnt5a-Ror signaling network, suggested a mechanism by which noncanonical Wnt signals impinge on the cytoskeleton to control morphogenetic cell behaviors, and identified potential chemical modulators of the pathway.

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**IN VIVO ANALYSIS OF EGFR FAMILY SIGNALLING AS A BYPASS MECHANISM IN PROSTATE CANCER**

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**BACKGROUND:** Prostate cancer (PCa) cells are reliant on androgenic ligands and the androgen receptor (AR) for their growth and survival, making AR inhibition a predominant therapeutic strategy for this type of cancer. Some prostate tumors however eventually fail this therapy because of ‘bypass’ mechanisms that emerge as a result of prolonged AR targeting. The present in vivo study was undertaken to assess the expression and activation of the epidermal growth factor receptor (EGFR) family (whose role is well-documented in PCa) in response to androgen deprivation therapy (ADT).

**METHODS:** Nude mice were implanted (s.c.) with CWR22 tumors (human-patient-derived, androgen-dependent ‘AD’) and its castration-resistant (‘CR’) subline CWR22-Rv1 (relapsed CWR22). Androgen deprivation (i.e. AR inhibition) was achieved by surgical or ‘sham’ castration of mice. Tumors were analyzed (immunohistochemistry/immunoblot) for EGFR/ErbB2/ErbB3/AR proteins and proliferative/apoptotic markers.

**RESULTS:** Castration caused significant tumor regression in AD but not CR tumors. An in vitro viability assay demonstrated that castration (mimicked by the use of charcoal-stripped serum, ‘css’) did not slow down CR cells to the same degree as it did AD cells. At baseline, intratumoral EGFR protein appeared unchanged in R22 tumors, ErbB2 levels decreased and ErbB3 protein increased in Rv1 tumors. Castration increased ErbB3 but not EGFR or ErbB2 proteins in CWR22 tumors. Phosphorylated forms of these receptors were generally difficult to detect but there was more phosphorylated ErbB3 protein in Rv1 tumors. With respect to baseline levels of downstream targets of the EGFR family, there was less phosphorylated Erk but not Akt protein in CWR22-Rv1 tumors. Castration decreased Erk protein in AD tumors but increased it in CR tumors. Quantification of immunohistochemical staining revealed that cytoplasmic EGFR and ErbB3 proteins were elevated in CR tumors but reduced in AD tumors. Castration greatly decreased Ki-67 staining in AD but not in CR tumors while the number of TUNEL-positive nuclei and intensity of PARP staining decreased in castrated CR but not in AD tumors. ErbB3 and AR proteins were significantly correlated with DNA damage and proliferation in CWR22 tumors but only nuclear AR levels and proliferation were significantly correlated in CR tumors.

**CONCLUSIONS:** We conclude that androgen deprivation therapy may alter EGFR and ErbB3 protein levels and localization in androgen-dependent and castration-resistant tumors. The EGFR family is typically activated at the cell surface hence their presence and activity there, in response to castration, may initiate signalling pathways encouraging tumor cell proliferation and survival.
A PERSONAL HEALTH NETWORK FOR CHEMOTHERAPY CARE COORDINATION: EVALUATION OF USABILITY AMONG PATIENTS

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Cancer is a top concern for the United State and globally. Cancer care suffers from lack of coordination, silos of information, and high cost. Interest is emerging in developing formalized coordination of care in cancer to address these challenges. Person-centered technology can support movement by improving coordination and thereby improving the lives and health of individuals with cancer. An interprofessional team has developed the "personal health network" (PHN) in pursuit of this goal. The PHN is a new solution leveraging social networking and mobile technologies, among individuals undergoing chemotherapy and receiving care coordination, implemented as part of a small (n=60) two arm, randomized, pragmatic trial at UC Davis Comprehensive Cancer Center. Interviews using think aloud methodology were conducted with the first 12 participants from the intervention arm. Early results suggest that participants feel more connected to the healthcare team using the PHN, find value in access to the patient education library, and are better able to organize the many activities that occur during chemotherapy. Improvements are needed in reconciling overlaps with information in the MyChart personal health record, clarity of navigation and locating specific functions, and inconsistent connectivity. Findings contribute to improvements in version 2 of the PHN and informs a roadmap for potentially greater impact in technology-enabled cancer care coordination.

CLINICAL PREDICTORS OF SURVIVAL IN SMALL CELL LUNG CANCER (SCLC) PATIENTS <50 YEARS OF AGE: RESULTS FROM THE CALIFORNIA CANCER REGISTRY

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Background: SCLC is an often lethal disease that commonly occurs in older individuals with a history of heavy tobacco use. Limited epidemiologic and outcomes data are available for young SCLC pts (< 50 years of age). We analyzed the CCR to explore the clinical variables related to cause specific survival (CSS) of young pts. Methods: SCLC pts diagnosed between 1998-2012 were included. Primary outcome was CSS. Hazard ratios (HR) for CSS were calculated using Cox Proportional Hazards (PH) models for all ages & for pts <50 years, adjusted for baseline variables: age, gender, stage, race, year of diagnosis, treatment, socioeconomic status (SES), and location (urban vs. rural). Results: We identified 22,863 SCLC pts, of which 975 were <50 years of age (4.2%). Demographics for pts <50 years: Males-51%; White-71%; Stage IV-60%; Chemotherapy-79%; Urban location-92%; high SES-22%. Fewer pts < 50 years were diagnosed in later years: from 40% in '98-'02 to 24% in '08-'12. Results of multivariate Cox PH models are shown (see below). Conclusions: Age < 50 years was an independent predictor of improved CSS (HR 0.82, p<0.0001). In younger pts, female sex (HR 0.81, p=0.0045), Asian race (HR 0.57, p=0.0075), and rural residence (HR 0.75, p=0.042) were associated with better CSS, among other variables.
**DETERMINANTS OF SURVIVAL IN ADOLESCENTS AND YOUNG ADULTS WITH UROTHELIAL BLADDER CANCER: RESULTS FROM THE CALIFORNIA CANCER REGISTRY**

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**Background:** Bladder cancer (BC) is a common malignancy and is often diagnosed in the elderly. Previous studies have reported racial disparities in survival outcomes in BC patients but have not focused on a younger demographic. We sought to identify factors influencing cancer-specific survival (CSS) in adolescents and young adults (AYA, ages 15-39) with BC using the California Cancer Registry (CCR).

**Methods:** Patients diagnosed with BC between 1998 through 2012 and reported to the CCR as of October 2013 were included. The primary outcome measure was CSS. Cox regression models were used to evaluate predictors of improved CSS in AYA patients with BC, adjusted for potential confounders, including race and socioeconomic status (SES, scaled from lowest to highest, 1-5).

**Results:** Of 111,800 cases of BC, we identified 1,753 AYA patients. Age distribution (n, %) was as follows: 15-19 (47, 2.7%), 20-24 (113, 6.4%), 25-29 (216, 12.3%), 30-34 (456, 26.0%), & 35-39 (921, 52.5%). Most were male (1,284, 73.2%), white (1,162, 66.3%), had in situ/localized stage (1,549, 88.3%), and had transitional cell histology (1,608, 91.7%). Bivariate analysis showed worse CSS in females (Hazard Ratio [HR] 1.64, p=0.007), African Americans (HR 2.9, p<0.001), and distant stage (HR 278.210-3, p<0.001), among others. Multivariable analysis demonstrated that African American race (HR 2.93.02, p=0.0010007), distant stage (HR 269.64.9, p<0.001), and low SES (HR 2.51.72, p=0.000752) were significant predictors of poor CSS. Interaction analysis showed that African Americans in the lowest SES groups (i.e., SES 1-3) had significantly worse CSS (HR 5.03, p=0.05045) than white patients, but there was no difference between other race groups at in either SES group.

**Conclusions:** Racial and socioeconomic disparities exist in AYA patients with BC diagnosed in California. Potential causes of these disparities could include genetic differences and lack of access to quality cancer care. Further studies are warranted to further identify the underlying causes in order to overcome these disparities.
**SWOG 0709: RANDOMIZED PHASE II TRIAL OF ERLOTINIB VS. ERLOTINIB PLUS CARBOPLATIN/PACLITAXEL IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER AND IMPAIRED PERFORMANCE STATUS AS SELECTED BY A SERUM PROTEOMICS ASSAY**


UC Davis Comprehensive Cancer Center (PNL, PCM, DRG); SWOG Statistical Center, Seattle, WA (JM, MWR); Lahey Hospital & Medical Center, Burlington, MA (PJH); University of Kansas Cancer Center, Kansas City, KS (SKW); University of Utah Medical Center, Salt Lake City, UT (WLA); and the University of Colorado, Denver, CO (FRH)

**Background.** Advanced stage non-small cell lung cancer (NSCLC) patients with borderline performance status (PS2) are often excluded from clinical trials and platinum-based therapy. In light of the potential role for serum proteomics in predicting erlotinib benefit beyond that of EGFR mutational status, we conducted a trial of erlotinib +/- chemotherapy in a cohort of PS2 NSCLC patients enriched by the Veristrat proteomics assay.

**Methods.** Metastatic NSCLC PS2 patients with acceptable end-organ function and Veristrat-good status were randomized to either erlotinib 150 mg orally daily (Arm 1) or erlotinib 150 mg orally daily on days 2-16 plus 4 cycles of carboplatin (AUC 5 day 1) and paclitaxel (200 mg/m2 IV day 1), followed by erlotinib 150 mg orally (Arm 2). Arm 2 agents were pharmacodynamically separated to mitigate potential antagonism. The arm with superior observed median progression free survival (PFS) would be selected for further evaluation, but only if ≥ 3 months.

**Results.** The trial terminated prior to the planned accrual of 98 patients for regulatory reasons. Of 156 patients screened, 83 (59%) were classified Veristrat-good; 59 met trial eligibility and were randomized (Arm 1- 33; Arm 2- 26). Arm 2 patients had higher response rate (23% vs. 6%, p=0.06), disease control rate (77% vs. 41%, p=0.0046), median PFS (4.6 vs. 1.6 months, p=0.06), and median overall survival (11 vs. 6 months, p=0.27). Treatment-related grade 4 adverse events were seen in 2 patients in Arm 1 (thrombosis, hypomagnesemia) and 5 patients in Arm B (neutropenia in 5, febrile neutropenia in 1, leukopenia in 1).

**Conclusion.** In a proteomics-enriched cohort of PS2 patients with NSCLC, pharmacodynamically-separated erlotinib plus chemotherapy, when compared to erlotinib alone, had better efficacy and surpassed the protocol-specified benchmark of PFS > 3 months required for further study.

*This investigation was supported in part by the following PHS/DHHS grant numbers awarded by the National Cancer Institute (NCI), National Clinical Trials Network (NCTN): CA180888, CA180819, CA180846, CA180818, CA180830; by the NCI Community Oncology Research Program (NCORP): CA189821, CA189971, CA189953, CA189830, CA189822, CA 189872, CA 189858; and in part by Biodesix and Genentech.*
OUR FEATHERED FRIENDS: PIGEONS (COLUMBA LIVIA) AS TRAINABLE OBSERVERS OF PATHOLOGY AND RADIOLOGY BREAST CANCER IMAGES

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Pathologists and radiologists spend years acquiring and refining their medically essential visual skills, so it is of considerable interest to understand how this process actually unfolds and what image features and properties are critical for accurate diagnostic performance. We have found that pigeons (Columba livia)—which share many visual system properties with humans—can serve as promising surrogate observers of medical images, a capability not previously documented. These birds were able to learn to distinguish non-malignant from malignant breast pathology images, as well as non-malignant from malignant microcalcifications (from mammograms) using a training-set, test-set study format, while failing to generalize discrimination behavior when tested on a much harder chest x-ray task. The pigeons’ discrimination skills are independent of brightness and color variations, and the diagnostic performance seems to approximate that of human observers. We suggest that pigeons as experimental subjects can shed fresh light on important image properties in medical diagnostics, and can be used to assess the effects of image acquisition, processing, compression, and other manipulations on achievable diagnostic performance by humans (and possibly computers too).

INCREASING TRENDS OF KIDNEY AND RENAL PELVIS CANCER IN CALIFORNIA

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Background: The incidence of kidney cancer (KC) in California has increased markedly over the past 2 decades, although mortality rates have largely remained stable. Primary risk factors for KC include smoking, obesity, hypertension, and long-term dialysis. Changes in the population prevalence of primary risk factors for KC and improved sensitivity or greater utilization of diagnostic tests could explain the increased incidence of the disease.

Purpose: This study sought to examine trends and possible reasons for the rising incidence of KC in California.

Methods: Joinpoint KC incidence trends from 1988-2011 were estimated by sex, race/ethnicity, and stage at diagnosis. Trends in the prevalence of tobacco use, obesity, and high blood pressure in California were obtained from CDC’s BRFSS data. Literature review was conducted to evaluate the use of imaging tests.

Results: KC incidence in California increased since 1988 in both sexes and among all racial/ethnic groups, by 42% in the past decade only. Survey data show that while smoking has declined sharply in California since 1988, the prevalence of obesity increased from 15.1% to 24.7%, and hypertension from 22.1% to 25.7%, between 1995 and 2010. The increase in KC incidence has been limited largely to localized tumors, which increased significantly by 3.1% per year until 2000 and by 7.6% per year until 2008. Incidence of regional stage disease increased by 1.2% after 1995, and metastatic cases did not increase. Use of MRI, CT, and nuclear medicine diagnostic methods has increased by several fold since 1988.

Conclusion: While an increase in population obesity may account for some of the rising incidence of kidney cancer, the fact that the majority of the increase in reported cases is accounted for by early-stage disease suggests that the increased incidence of kidney cancer in California is largely attributable to greater utilization of advanced diagnostic imaging methods and earlier diagnosis of tumors.
QUALITY OF CARE AND OUTCOMES AMONG CANCER PATIENTS IN CALIFORNIA ACCORDING TO SOURCE OF HEALTH INSURANCE

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Background: Approximately $260 billion is spent annually in the U.S. diagnosing and treating cancer. Aging of the population, rising life expectancy, and increased population obesity, among other things, will substantially increase these costs in coming years. Despite generally improved cancer treatment, population disparities in the quality of cancer treatment and survival according to source of health insurance have been previously found.

Purpose: This study sought to evaluate differences in stage at diagnosis, quality of treatment and survival among cancer patients in California according to type of health insurance.

Methods: Persons with a diagnosis of breast, lung, colon, rectum, or prostate cancer during the period 2004-2012 were identified in the California Cancer Registry. Descriptive statistics on stage at diagnosis and 5-year relative survival by insurance coverage were generated. Cancer treatment across categories of insurance coverage was evaluated using the Commission on Cancer quality measures.

Results: Persons insured by Medicaid at the time of diagnosis were more likely to be diagnosed at later stages across all five cancer types. Approximately 25% of Medicaid members with breast cancer were diagnosed at late stage compared with 11% of patients having private insurance. Medicaid members also had poorer survival than patients with private insurance across all cancer types. Higher proportions of persons with breast, colon, and rectal cancer having VA insurance received recommended treatment compared to those with other types of insurance.

Conclusions: Significant differences exist in stage at diagnosis, treatment and survival among cancer patients in California according to their source of insurance coverage. The analysis was limited by the variable quality of payer source information in the CCR. These findings will be further examined through linkage with Medicaid enrollment files.

LRIG1 STRUCTURE-FUNCTION ANALYSIS

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The epidermal growth factor family of receptor tyrosine kinases is composed of four members: EGFR, ErbB2, ErbB3, and ErbB4; these are membrane bound proteins that control important cell functions including cell cycle progression and differentiation. Deregulated expression of the ErbB family by gene amplification and/or protein over-expression is associated with the development of a variety of cancer types.

The tumor suppressor, LRIG1 is a transmembrane protein which contains 15 leucine-rich repeats (LRR), immunoglobulin like (Ig) domains, a single transmembrane domain and a large cytoplasmic domain of unknown function. LRIG1 can directly interact with all members of the ErbB family, leading to receptor internalization and subsequent receptor degradation. However, LRIG1 mechanism of action remains unknown. LRIG1 belongs to the LRIG family that in vertebrates is composed by two other members, LRIG2 and LRIG3, whose function differs from LRIG1.

It has been shown that either the LRR or the Ig domains are sufficient to drive LRIG1- ErbB interaction. Furthermore, removing the entire cytoplasmic tail of LRIG1 does not affect its function, suggesting that the functional domain is located at the extracellular portion of the protein.

Recently, we identified the existence of different LRIG1 variants; these isoforms are lacking some of the LRRs. These LRIG1 variants are unable to decrease the receptor expression levels,
indicating that the missing LRRs on the isoforms are essential for LRIG1 negative regulation function.

Here, we show that LRIG1 activity is transferable among the LRIG members. Moreover, using a series of LRIG1 deletion constructs we localize a segment of 52 amino acids, which removal results in loss of LRIG1 activity, suggesting that LRIG1 function resides within this small fragment. Identifying the LRIG1 functional domains represents a big advantage towards elucidating LRIG1 mechanism of action, which can ultimately help to the development of better cancer treatments.

**EPOXY EICOSANOIDS (EETS) YIELD A PROANGIOGENIC METABOLITE, THE HYDROXY EET, THROUGH OXYGENATION BY CYCLOOXYGENASE**

*Amy Rand, Bogdan Barnych, Kin Sing Lee, Bruce Hammock*

Arachidonic acid is an essential omega-6 fatty acid which metabolizes through several enzymatic pathways to produce an array of biologically important metabolites. One class of metabolites formed from CYP450 epoxygenases is the epoxy eicosanoids (EETs), which are anti-inflammatory, analgesic, and anti-hypertensive. However, EETs have also been shown to enhance angiogenesis, a process involved in cancer tumor growth. EETs undergo further metabolism by soluble epoxide hydrolase (sEH) to dihydroxy eicosanoids, therefore inhibition of sEH leads to increased angiogenesis and tumor growth. Surprisingly, inhibition of both sEH and COX resulted in significant decrease in this activity, suggesting that the angiogenic activity of EETs may be attributed to downstream metabolites formed from COX. This study explores the fate of EETs with COX and elucidates whether the resulting metabolites are angiogenic. One of these metabolites, the hydroxy-EET, was synthesized in our lab and the in vivo Matrigel plug assay was used to evaluate its effect on angiogenesis in mice. Matrigel plugs separately containing the hydroxy-EET, EETs, and angiogenic growth factors were implanted into mice and retrieved after 6 days to determine angiogenic response. All groups showed increased migration of fibroblasts and endothelial cells required for blood vessel formation. Evidence of capillary and blood vessels were also observed for each treatment, quantified using H&E and CD31 staining. This suggests that the hydroxy-EET has a direct role in stimulating angiogenesis, which may be directly associated with cancer tumor growth.
THE EFFECT OF AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) ON SURVIVAL IN CALIFORNIANS WITH MULTIPLE MYELOMA (MM) IN THE ERA OF MODERN TREATMENT

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Background: The use and timing of ASCT on survival after MM in the era of modern therapy remain topics of debate. Using population based data, we evaluated factors associated with the receipt of ASCT and the effect of ASCT on overall survival (OS).

Methods: Patients diagnosed with MM during 2000 – 2012 were identified in the California Cancer Registry (CCR) (n=12,714). CCR data were linked to the California Patient Discharge Database (PDD). Logistic regression estimated the odds ratio (OR) of having an early (< 1 year from diagnosis) or late (> 1 year) ASCT (vs. no ASCT). OS was calculated using the Kaplan-Meier (KM) method. To determine the effect of ASCT on OS from diagnosis date, Cox regression models estimated adjusted hazard ratios (aHR) of death treating ASCT as a time dependent covariate. OS time was compared after matching ASCT to no ASCT patients on age, sex, race/ethnicity, neighborhood socioeconomic status (SES), comorbidity at diagnosis, year of diagnosis, and accounting for time to transplant.

Results: The majority of MM patients were male (54%) and of non-Hispanic white (58%) race/ethnicity; 19% Hispanic, 12% African American, and 9% Asian. Median age at diagnosis was 67 (range 18 – 104). African Americans and Hispanics were younger than non-Hispanic whites (median age 64 and 65 vs 69). Comorbidity data from the PDD was available in 59% of the patients in the 2 years prior to MM diagnosis: 7.5% had 0, 21% had 1-2, and 31% had ≥3 comorbidities.

A total of 2136 (17%) patients underwent ASCT: 1347 < 1 year from and 789 ≥1 year after diagnosis. Time to ASCT did not change over time: among patients diagnosed 2000 – 2003 median time to transplant was 9.2 mo, 10 mo among those diagnosed 2004 – 2007 and 9.7 in those diagnosed 2008 – 2012. Patients who underwent ASCT were younger than those who did not (median age 56 vs 70 respectively). African Americans were less likely to undergo early ASCT (OR 0.7, P<0.001), but not late ASCT (OR 0.8, P=0.07). Patients with ≥3 comorbidities (vs. 0) at diagnosis were less likely to have ASCT (OR 0.42 P<0.001 and OR 0.28 P<0.001 for early and late, respectively), while patients with 1-2 comorbidities were less likely to have late ASCT (OR 0.59 P<0.001). The lowest 2 quintiles of SES was associated with less use of early ASCT (OR 0.62 p<0.001 and 0.65 p<0.001 respectively), but not late ASCT (OR 0.89 p=0.4 and 0.96 p=0.7 respectively). The likelihood of receiving ASCT increased over time: compared to 2000-2003, the ORs for patients diagnosed in 2004 – 2007 were 1.36 for early (P<0.001) and 1.64 (P<0.001) for late ASCT and were 2.64 (P<0.001) for early and 1.80 (P<0.001) for late for those diagnosed in 2008-2012.

The median follow-up was 32 months. Median OS from diagnosis for the entire cohort, unadjusted for age, comorbidities, and SES was 37 months. Adjusting for sex, race/ethnicity, age at diagnosis, SES, comorbidities, insurance status and year of diagnosis, OS improved over time: compared to patients diagnosed in 2008 – 2012, aHR of death of those diagnosed 2000-2003 was 1.58 (P<0.001), and 1.35 (P<0.001) for those diagnosed 2004-2007. ASCT at any point was associated with a 23% reduction in the risk of death from all causes (aHR 0.77 P<0.001). Patients who received early ASCT had a 27% reduction (aHR 0.73 P<0.001), while those receiving late ASCT had an 11% decrease (aHR 0.89 P<0.001) in risk of all cause death. In the matched analysis, the median OS from date of transplant, or matched date in the no ASCT cohort, were: no ASCT = 49 mo, early ASCT = 83 mo, and late ASCT 65 mo (P<0.001 Figure 1). The effect of aSCT on OS differed by date of diagnosis (P for interaction <0.001). Improvements in OS due to ASCT were more pronounced in later time periods: aHR for early and late ASCT in 2000-2003...
were 0.9 (P = 0.12) and 0.98 (P = 0.86) compared with those in 2004-2007 (0.63 P<0.001 and 0.85 P = 0.06) and in 2008-2012 (0.55 P<0.001 and 0.74 P=0.08).

**Conclusions**: ASCT was utilized in 17% of Californians with MM during 2000-2012, and its use increased over time. The use of ASCT, whether within a year of diagnosis or later in the disease course, is associated with improved OS and this effect may be more pronounced in the era of novel agents. Despite the inherent limitations of analyses of administrative databases, the large number of patients and established robust nature of CCR and PDD data makes accurate depiction of results in the community probable. These data support the continued role of ASCT in the management of patients with MM.

Figure - Overall Survival of Multiple Myeloma patients after Transplant in California, 2000-2012

<<22>> PILOT STUDY OF KERNEL-BASED DYNAMIC 18F-FLUDEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY (KBD FDG-PET) FOR DETECTION OF LYMPH NODE METASTASES IN RECTAL CANCER PATIENTS TREATED WITH CHEMORADIATION THERAPY

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**Background**: Since 2004, neoadjuvant chemoradiation has been the preferred initial treatment for clinical stage II and III rectal adenocarcinoma. As compared to a surgery first approach, neoadjuvant chemoradiotherapy reduces the risk of local recurrence but results in reduced lymph node retrieval at the time of surgery. Residual positive lymph nodes despite neoadjuvant therapy are an important predictor of poor outcome; however, non-invasive assessment of lymph nodes in the mesorectum is challenging due to their size and location. Because static uptake of fludeoxyglucose (FDG) is not cancer specific, standard FDG Positron Emission Tomography (PET) cannot differentiate malignancy from certain benign conditions. Dynamic PET imaging acquires images at multiple time points and enables parametric imaging of FDG kinetics, providing fundamental quantitative information about the molecular process of glucose metabolism. The major limitation of standard dynamic PET, high noise due to low-counting statistics, has been overcome by a novel kernel-based image reconstruction method developed at UC Davis. The
resulting kernel-based dynamic (KBD) PET method demonstrated a five-fold gain in signal-to-noise ratio when tested on a small group of patients with breast cancer. We hypothesize that the combination of quantitative glucose transport (K1), which correlates with blood flow, and glucose utilization data (Ki) from KBD FDG-PET is suited to the task of distinguishing malignant lymph nodes from non-malignant or inflammatory nodes in rectal cancer patients treated with neoadjuvant therapy. We designed this pilot study to identify the changes in KBD FDG-PET assessed regional lymph node involvement induced by rectal cancer chemoradiation therapy and to estimate the accuracy of KBD FDG-PET to predict pathologic nodal status in clinically node positive rectal cancer treated with neoadjuvant chemoradiation.

**Methods:** Eligible patients with clinically node positive rectal cancer will have a baseline KBD FDG-PET along with the standard diagnostic imaging studies prior to standard 5-FU-based long course chemoradiation treatment. Just prior to surgical resection, approximately 4 and 8 weeks after completion of chemoradiation therapy, patients will undergo a second KBD FDG-PET. Tumor resection will occur according to standard practice, generally between 5 and 8 weeks after completion of chemoradiation therapy. Resection specimens will be subjected to standard pathologic assessment followed by staining of candidate lymph nodes for micrometastases. The primary endpoint is detection of a reduction in the number of positive lymph nodes assessed by KBD FDG-PET after chemoradiation therapy as compared to the pretreatment study. The secondary endpoint is the accuracy of KBD FDG-PET in classifying pathologic node negative or node positive rectal cancer after neoadjuvant therapy. Comparisons between KBD FDG-PET findings and the size of pathologically identified positive nodes and newly identified micrometastatic deposits are exploratory endpoints. This study has been IRB approved and activation is expected shortly.

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<<23>> A BIOINFORMATIC CORES ROLE IN CANCER GENOMICS

*Matthew Settles, PhD*

[No abstract submitted at time of print]

<<24>> TCGA AND IN VITRO FUNCTIONAL STUDIES SUGGEST CD22 MAY FUNCTION AS AN IMMUNE CHECKPOINT INHIBITOR IN MULTIPLE TUMOR TYPES.

*Sidhu RS, Barisone GA, Abuhay M, O'Donnell RT, Tuscano JM*

CD22 is a transmembrane receptor primarily expressed on B cells. Here we show the presence of CD22 on various solid tumors and its potential function in immune cell inhibition. Gene expression data obtained from The Cancer Genome Atlas (TCGA) reveals a significant number of solid tumors that express CD22 at high levels. Through the use of Kaplan-Meier plots and Cox Proportional Hazards analysis we were able to show that patients with CD22(+) tumors show decreased survival and higher rates of recurrence. Quantitative flow cytometry was used to confirm intra and extracellular CD22 expression levels obtained from their respective gene expression data. Furthermore, co-culture of lung (and other) cancer cells with activated (IL-2) PBMCs resulted in increased surface levels of CD22; this was more evident in cells with a large intracellular pool of CD22. Our work suggests that the presence of CD22 on solid tumors serves as a defense mechanism that may be mediated by the inhibition of T and NK effector cells.
LRIG1 (leucine-rich repeat and immunoglobulin-like domain containing), a member of the LRIG family of transmembrane leucine-rich repeat-containing proteins, is a negative regulator of receptor tyrosine kinase signaling and a tumor suppressor. LRIG1 expression is broadly decreased in human cancer and in breast cancer and low expression of LRIG1 has been linked to decreased relapse-free survival. Recently, low expression of LRIG1 was revealed to be an independent risk factor for breast cancer metastasis and death. These findings suggest that LRIG1 may oppose breast cancer cell motility and invasion, cellular processes that are fundamental to metastasis. However, very little is known of LRIG1 function in this regard. In this study, we demonstrate that LRIG1 is downregulated during epithelial-to-mesenchymal transition (EMT) of human mammary epithelial cells, suggesting that LRIG1 expression may represent a barrier to EMT. Indeed, depletion of endogenous LRIG1 in human mammary epithelial cells expands the stem cell population, augments mammosphere formation and accelerates EMT. Conversely, expression of LRIG1 in highly invasive Basal B breast cancer cells provokes a mesenchymal-to-epithelial transition accompanied by a dramatic suppression of tumorsphere formation and a striking loss of invasive growth in three-dimensional culture. LRIG1 expression perturbs multiple signaling pathways and represses markers and effectors of the mesenchymal state. Furthermore, LRIG1 expression in MDA-MB-231 breast cancer cells significantly slows their growth as tumors, providing the first in vivo evidence that LRIG1 functions as a growth suppressor in breast cancer.

As the demand for more sensitive and accurate biomarkers with predictive or prognostic utility grows, so does the need for integrating basic research, high-quality biospecimen collection, and the development of strong collaborations between academic researchers and industry.

The Molecular Pharmacology Shared Resource (MPSR) serves as a single point of contact for UC Davis Comprehensive Cancer Center-associated researchers interested in developing and testing novel agents and biomarkers in the clinical trials setting. Our services support a bench-to-bedside-to-bench approach to clinical translational research, from concept development via preclinical therapeutic modeling, assay development, protocol design, biospecimen collection and storage, correlative investigations of patient samples, and data analysis.

Preclinical modeling carried out by the MPSR includes both in vitro studies of novel anticancer regimens as well as a productive collaboration with The Jackson Laboratory (JAX) to conduct studies in patient-derived xenografts (PDXs). Clinically, the MPSR works in collaboration with the Office of Clinical Research (OCR) to support an average of 150 clinical trials annually, including the development of specimen collection procedures, clinical trial protocol language, the collection and processing of over 3000 patient specimens annually and the release of specimens to protocol-defined researchers. Our facilities utilize a customized specimen-tracking software package (Freezerworks Unlimited) to securely record and track all pertinent information on each
specimen. This software meets all state and federal standards for health information databases, including 21 CFR Part 11 and HIPAA, and allows us to provide detailed, timely and accurate specimen reports. For UCDCC researchers, the MPSR also manages and conducts correlative analysis of clinical trial specimens, closing the loop on the trial and helping to define a framework for further investigation.

Overall, the MPSR achieves its goals of providing user-friendly translational support for clinical trials at UCDCCC, with assistance to researchers at all steps of protocol development, from initial conception to final publication. The MPSR manages all of your clinical trials blood specimens from collection to analysis, and is highly responsive to all investigator and sponsor needs. Our close collaborations with outside researchers, industry, and within the UCDCCC provide a unique opportunity to carry out a wide range of correlative research, ranging from small phase I investigator-initiated studies to large, randomized phase III trials.

<<27>> WHAT THE PMCID?!? HOW TO STAY COMPLIANT WITH THE NIH PUBLIC ACCESS POLICY AND NOT LOSE YOUR FUNDING

Sonal J. Desai and Melanie Bradnam

Are you confused about PMCID? Has your funding been denied or delayed from NIH because you were not in compliance? NIH's public access policy requires all peer-reviewed manuscripts that arise from NIH funding, and which were published on or after April 7, 2008, be made available to the public within 12 months of the publication date. This requires that investigators ensure their manuscripts are submitted to the NIH Manuscript Submission System, where it is assigned a PMCID. This is not the same as a PMID. There are several methods and steps for this process which can often be confusing. Sometimes the journal will submit it on behalf of the investigator and sometimes they won’t. However, it is always the investigators responsibility to make sure their publications are compliant. NIH is now cracking down on this policy, and if your publications are not compliant, your funding will be held up and/or denied until all your non-compliant publications have PMCID numbers. To find out more and get clarification on the different submission processes, stop by our poster!
IDENTIFICATION OF ACTIVE COMPONENTS OF GENISTEIN COMBINED POLYSACCHARIDE THROUGH FRACTIONATION, BIOASSAY, AND MASS SPEC ANALYSIS

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BACKGROUND: A novel aglycone isoflavone-rich extract (genistein combined polysaccharide [GCP]) produced by culturing soybean extract with mycelia from the mushroom Ganoderma lucidum, is mostly comprised of the deglycosylated isoflavones genistein, daidzein, and glycitein. Our previous studies demonstrated GCP has low toxicity in patients, and is able to inhibit AR and Akt activity in prostate cancer cell lines and thereby promote cell cycle arrest and apoptosis. The goal of the present study was to identify which components of GCP are responsible for this activity.

METHODS: GCP was generously provided by Amino Up Chemical company, Ltd. Reverse-Phase HPLC was carried out to fractionate GCP, and fractions were tested on LCMS. The impact of the different fractions versus crude GCP, genistein, daidzein, glycitein, and a vehicle control on cell proliferation was evaluated using the MTT assay. UPLC-Mass Spec was used to quantify the steroid composition of GCP treated and untreated LNCaP cells and thereby determine whether GCP affected steroid metabolism.

RESULTS: GCP was fractionated into 60 fractions. MTT assay showed that out of these 60 fractions, two fractions (Fr.37 and Fr.40) inhibited cell proliferation. LCMS identified fraction 40 as mainly genistein and the fraction 37 as mainly a mixture of daidzein and glycitein. MTT assay showed that 90% of the activity exhibited by GCP was contributed by fraction 40 and the rest mostly by fraction 37. Steroid composition analysis of LNCaP treated with GCP versus vehicle demonstrated GCP mediates a 3-fold decrease in testosterone level and reduced epitestosterone levels to zero.

CONCLUSIONS: Our combined data demonstrate that 90% of the activity exhibited by GCP is contributed by genistein and remaining 10% is contributed by glycitein and daidzein. Steroid composition analysis indicates GCP can reduce testosterone production.

FUTURE DIRECTIONS: We will perform Western blotting to determine whether Fr.37 and Fr.40 are responsible for mediating the inhibition AR and Akt activity which is observed in GCP-treated prostate cancer cell lines. Steroid composition analyses will be conducted to determine the contribution of these fractions to inhibition of testosterone production.

HER2-NF-KB-CONTROLLED CD47 EXPRESSION RESULTS IN ENHANCED TUMOR SELF-DEFENSE AND RADIRESISTANCE

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Immune tolerance towards malignant cells is responsible for tumor progression and metastases. Despite their immunogenecity, cancer cells develop sophisticated mechanisms by which they are able to neutralize and/or evade the immune-surveillance. Recently, the overexpression of CD47 has been suggested to participate in the immune escape protocol in several malignancies.
However, the regulation of CD47 expression, especially in response to radio- or chemotherapy, is currently unknown. Here, we found that CD47 is overexpressed in breast cancer cells and breast cancer stem cells, and its expression was further enhanced in response to radiation. The expression of CD47 was found to be regulated by NF-κB through its binding element found in the CD47 promoter, both via luciferase gene reporter and ChIP assays. Interestingly, CD47 expression correlated with HER2 expression in breast cancer; and HER2 was found to be an upstream regulator of CD47 expression. Herceptin or Lapatinib treatments significantly reduced CD47 expression, and enhanced phagocytosis via macrophages. Furthermore, inhibition of CD47 resulted in reduced cell survival upon both anti-HER2 and radiation treatments. Without CD47 activity, the HER2-positive breast cancer cells were less aggressive, invasive and radioresistant. Taken together, these data suggest that CD47 expression is a biomarker for breast tumor aggressiveness and resistance, and represents a potential target to treat breast tumor during radio- or chemotherapy.

CHARACTERIZING PROSTATE CANCER BONE METASTASIS USING TISSUE ENGINEERED MATRICES

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Purpose: The American Cancer Society estimates ~28,000 men will die mostly from advanced prostate cancer (PCa) bone metastasis in 2015. The preferential localization of PCa to the skeleton indicates that metastasis is enhanced by PCa cellular response to chemical cues from the bone microenvironment (bone organic matrix). The molecular mechanism of this process is unclear. We propose using tissue engineering with cell and molecular biology assays to identify novel factors critical for PCa cell migration, osteomimicry and secondary tumor formation.

Methods: To mimic the organic matrix, we created de-cellularized matrices (DM) from human BM-MSCs and osteoblasts (NHOst), and treated the DM with enzymes (eDM) to abolish formation of glycosaminoglycans (GAGs), which are growth factor binding sites. The matrices were characterized with staining and protein analysis. Cell response towards DM and eDM was measured in non-osteotropic LNCaP, osteoblastic C4-2B and osteolytic PC-3 PCa cell lines. Migration to DM or eDM was measured through Boyden chamber assays.

Results: PCa cells showed heterogeneous migration to DM or eDM (Fig. 1). Osteoblastic C4-2B cells revealed significant migration to DM derived from both hMSCs and NHOst; while migration towards osteoblast-derived eDM was attenuated (Fig. 1A). Non-osteotropic LNCaP cells did not specially migrate to DM or eDM (Fig. 1B). Osteolytic PC-3 cells migrated slightly more towards DM over eDM, but this difference was not significant (Fig. 1C).

Alcian Blue staining showed reduced growth factor-binding glycosaminoglycans (GAGs) in eDM compared to DM for matrices derived from both cell sources (Fig. 2A). Micro BCA showed hMSCs deposited about 5-6 fold more total matrix protein than NHOst, but there was no quantitative difference between DM vs. eDM for either cell source (Fig. 2B). This was further supported qualitatively via Coomassie Blue staining (Fig. 2C). These data suggest DM and eDM only differ in GAG presence and not overall matrix deposition.

These continuing studies and future work will expose details on how PCa invades into the bone. This knowledge can lead to metastasis-inhibiting therapies that when combined with treatments targeting primary tumors will finally eradicate PCa.
INCREASED PHOSPHORYLATION OF EIF4E INDUCES RESISTANCE TO TREATMENT WITH MTOR INHIBITORS ALONE OR TOGETHER WITH AR ANTAGONISTS IN ADVANCED PROSTATE CANCER.

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The standard of care for patients with recurrent prostate cancer (PCa) is the use of androgen receptor (AR) antagonists, but the treatment ultimately fails, resulting in the development of castration resistant PCa (CRPC). Patients with CRPC are frequently found to continue to express an active AR, despite castration resistance, and AR inhibitors such as enzalutamide, remain effective in these patients for several months. We previously showed that upregulation of mammalian target of rapamycin (mTOR) activity upon use of AR antagonists contributed to acquired resistance to this therapy, and that a combination of an mTOR inhibitor and an AR antagonist overcame resistance to AR antagonists alone (Wang et al, Oncogene, 2008;27(56):7106-17). Based on our data, a Phase II clinical trial was conducted to determine the efficacy of the combination of the mTOR inhibitor RAD001 and the AR antagonist bicalutamide in bicalutamide-naïve CRPC patients (ClinicalTrials.gov Identifier: NCT00814788). This study, which was recently concluded, showed a response rate of 75% with this combination with the historical control of 25%. The overall goal of this project was to define pathways that results in resistance to combinations of mTOR and AR inhibitors in patients with CRPC.

Comparison of various mTOR inhibitors: the mTORC1 inhibitor RAD001, a mTORC1/C2 dual inhibitor INNK128 and a mTORC1/C2/PI3K triple inhibitor BEZ-235 either alone or in combination with AR antagonists bicalutamide and enzalutamide in various prostate derived cell lines including C4-2, PC-346C, 22Rv1 and CWR-R1, identified cells that were resistant (CWR-R1, PC-346C) vs those that were sensitive (22Rv1, C4-2) to these inhibitors. Investigation of the base-line molecular profile of these cells demonstrated that those that expressed high levels of the phosphorylated form of eIF4E (S209), a translation initiation factor activated downstream of mTOR phosphorylation, were resistant to mTOR inhibitors. Inhibition of eIF4E by siRNA upregulated p38MAPK activity and also increased the levels of the epidermal growth factor receptor (EGFR) and ErbB3, a member of the same family. Simultaneously, downregulation of eIF4E phosphorylation also resulted in sensitivity of CRPC cells to the combination of the mTOR inhibitors with AR antagonists. Investigation of the mechanism by which eIF4E phosphorylation levels increased in certain CRPC cells but not in others revealed that expression and transcriptional activity of the AR negatively correlated with the levels of eIF4E phosphorylation. In cells with high basal levels of phospho-eIF4E, bicalutamide further increased eIF4E phosphorylation, whereas those with low eIF4E levels were not further affected. The ability of AR inhibition to suppress eIF4E phosphorylation was mediated by MAP kinase interacting kinase (Mnk), and the ability of some cells to phosphorylate eIF4E, but not others, correlated with the levels of Mnk phosphorylation. Based on these studies, we predict that patients with high basal PSA who express low levels of Mnk phosphorylation are the ones who are likely to respond to the combination of a mTOR inhibitor and an AR antagonist.
Objective: Toxicity following thoracic radiotherapy (RT) is substantial. Functional lung avoidance that selectively avoids highly functional lung sub-regions may reduce toxicity. However, the temporal change in regional lung function throughout a course of RT is not well known. As a correlative imaging study embedded in a pilot clinical trial evaluating computed tomography (CT) ventilation functional image-guided RT for lung cancer, we obtain mid-treatment ventilation imaging at two time points to define temporal changes in regional ventilation and estimate the impact of adaptive RT (ART) strategies.

Materials and Methods: We have activated a single-institution, IRB-approved pilot clinical trial evaluating feasibility and safety of CT ventilation functional image-guided RT with a planned accrual of 20 patients. Two cohorts are eligible: 1) early stage non-small cell lung cancer (NSCLC) treated with SBRT and 2) Locally advanced (LA)-NSCLC treated to 60 Gy over 30 fractions. LA-NSCLC patients undergo 4DCT at pre-treatment simulation and mid-treatment following delivery of 16-20 and 30-34 Gy to evaluate temporal changes in regional ventilation. CT ventilation images are created by (1) 4D CT imaging, (2) deformable image registration for spatial mapping of the peak-inhalation 4D CT image (moving) to the peak-exhalation image (fixed), and (3) quantitative analysis of regional volume change, yielding a ventilation image. For each patient, CT ventilation functional image-guided ART plan, CT ventilation functional image-guided non-ART plan, and anatomical image-guided non-ART plans are generated and compared.

Results: Six patients have enrolled, 5 with LA-NSCLC. One patient was removed from protocol therapy prior to initiation of RT. CT ventilation functional image-guided RT plans have been successfully generated and implemented for the remaining patients. One LA-NSCLC patient has completed all protocol related therapy including two mid-treatment 4D CT scans, and three patients are on active treatment. In the one evaluable patient, recovery of regional ventilation was observed in the ipsilateral lung corresponding to tumor regression. The mean percentile ventilation value in the ipsilateral lung increased from 48.4 (pre-RT) to 51.5 (20 Gy) and 53.3 (32 Gy). Accrual of additional patients is ongoing.

Conclusions: Accrual to our pilot phase clinical trial evaluating adaptive CT ventilation functional imaged-guided adaptive RT is ongoing. Analysis of one patient suggests substantial temporal changes in regional lung ventilation during RT. Analysis of the full patient cohort once accrual is complete should provide valuable insight into ART strategies for functional image-guided lung cancer RT.
THE FLUORESCENCE LIFETIME TECHNIQUE FOR REAL-TIME ROBOTIC CANCER SURGERY GUIDE

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Fluorescence lifetime imaging has demonstrated to be a robust technique for tissue biochemical and/or functional characterization. Fiber based lifetime measurements present great potential for intraoperative diagnosis and guidance of surgical procedures. We report a novel real-time technique to co-register and display the measured fluorescence lifetime values with the corresponding measured tissue locations. This is achieved by overlapping a 450 nm aiming beam with the excitation light in a single delivery/collection fiber and by continuously imaging the region of interest with a color camera. The interrogated locations are then extracted from the acquired video frames via color-based segmentation of the aiming beam. Assuming a Gaussian profile of the imaged aiming beam, the segmentation results are fitted to ellipses that are dynamically scaled at the full width of three automatically estimated thresholds (50%, 75%, 90%) of the Gaussian distribution's maximum value. This enables the dynamic augmentation of the white-light video frames with the corresponding fluorescence decay parameters. The system has been integrated to the DaVinci Surgical System (Intuitive Surgical, Inc.). Specifically, we used a fiber introducer designed for laser ablation (5Fr EndoWrist Introducer). Its three degrees of freedom allows efficient aiming of the probe for any tissue. In addition, the endoscope of the FireFly Module is used as the imaging camera, providing real-time video streams through the use of a frame-grabber. These frames are then augmented with the reconstructed lifetime maps and projected in the Surgeon's Console via the TilePro Module in real time (~23 fps). Currently this technique is adapted for use during trans-oral robotic surgery to guide the surgeon during the tumor removal. Ongoing tests conducted in an in vivo swine model and human patients demonstrate the potential of this technique to delineate distinct tissue types including head and neck oral tumors in real-time.

BIOENGINEERING NOVEL CHIMERIC MICRORNA-34A AGENTS FOR CANCER THERAPY

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Cancer cells often show a dysregulation in microRNA expression profiles, generally exhibiting an upregulation of oncomirs and loss of tumor suppressors. Reintroducing tumor suppressive miRNA (e.g., miR-34a) into cancerous cells, namely miRNA replacement therapy, represents a new strategy for the treatment of cancer. However, development of miRNA replacement therapy is limited to the use of synthetic RNAs with artificial modifications. In this study we developed a novel approach towards large-scale biosynthesis of chimeric miR-34a agent in *Escherichia coli* using tRNA scaffold to better mimic naturally occurring post-transcriptionally modified RNAs. which may act as a prodrug for cancer therapy. This approach yielded milligram quantities of recombinant RNA from 1 L bacterial culture, which allowed for *in vivo* testing using human non-small cell lung cancer A549 and hepatocarcinoma HepG2 xenograft tumor mouse models. As a result, we demonstrated a significant downregulation of miR-34a target genes (CDK6, MET, SIRT1) as well as reduction of tumor size in a dose dependent manner. Furthermore, we monitored the metabolic fate of tRNA/mir-34a through deep sequencing and qPCR to reveal precise processing into
mature miR-34a, thus mechanistically producing specific tumor suppressive effect. In addition, we analyzed the acute effects of biologic miR-34a agent on blood chemistry profiles and IL-6 levels in mouse models, which showed no signs of toxicity. Therefore, we illustrate the efficacy and safety of recombinant miRNA agents that would be a new class of miRNA agents for pharmacotherapies.

<<8>> ELUCIDATING THE ROLE OF BHLHE40/DEC1/SHARP2/STRA13 IN PROSTATE CANCER

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BACKGROUND: Basic-helix-loop-helix proteins (BHLH) are transcription factors that form a large superfamily known to play important roles in critical developmental processes in many organisms by repressing the transcription of various target genes. Previous studies showed that overexpression of the BHLHE40 (also known as DEC1, STRA13 or SHARP2) transcriptional repressor results in growth suppression, cell cycle arrest, and cellular senescence indicating that BHLHE40 may have important tumor suppressor functions. Consistent with these observations, the expression of BHLHE40 is indeed downregulated in some tumors, such as in esophageal cancer. Intriguingly however, it is also overexpressed in many such as lung cancer, breast cancer. Our overall goal is to elucidate the function of BHLHE40 in prostate cancer (CaP) and gain an understanding of how it is regulated, and what it regulates in primary prostate tumors versus castration resistant prostate cancer (CRPC) cell lines.

METHODS: Initial studies were based on qPCR analysis to compare the expression levels of BHLHE40 in different cell lines ranging from androgen-dependent LNCaP cells to the castration resistant C4, C4-2, C4-2b, R1, Rv1, PC3 and PC3 cells that stably express the androgen receptor (AR) (PC3-AR). Further analysis were done by treating LNCaP and C4-2 cells with 1 nM dihydrotestosterone (DHT) in media containing fetal bovine serum (FBS), or charcoal stripped serum (CSS). Lysates of cells thus cultured were then subjected to Western blot analysis to check the level of BHLHE40 protein in these cell lines. Knock-down of AR, or the use of AR inhibitors Enzalutamide and/or Bicalutamide were used to further assess the regulation of BHLHE40 by the AR.

RESULTS: qPCR comparison of BHLHE40 transcript levels in LNCaP versus C4, C4-2, R1, Rv1, PC3 cells showed that while LNCaP cells have high transcript levels of BHLHE40, the CRPC cells all had very low transcript levels of this transcription factor. When comparing LNCaP to PC3 and PC3-AR cells, it was interesting to note that PC3-AR cells showed significantly higher transcript levels of BHLHE40 than PC3 implying that BHLHE40 may be regulated by the AR pathway. Treatment with 1 nM DHT on these cells showed that BHLHE40 increases over time following DHT treatment. In contrast, inhibition of AR by Enzalutamide (2 μM) showed reduced BHLHE40 levels, although Bicalutamide (10 μM) did not significantly altered the expression level of BHLHE40 in LNCaP cells.

CONCLUSIONS: Our results indicate that BHLHE40 is regulated by the AR pathway, although whether this is direct or indirect is yet to be determined. This observation is significant, since it indicates that the AR may be utilizing this transcription factor to suppress the transcription of other genes.

Future studies will attempt to determine if BHLHE40 may have an androgen-responsive-element (ARE) in its promoter and via ChIP assay to identify possible binding sites for AR in conjunction with luciferase assay to assess androgen-receptor mediated regulation.
FORCES BETWEEN INVASIVE CELLS AND ITS IMPLICATIONS ON COLLECTIVE CELL MIGRATION

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The first step of metastasis is the invasion of cancer cells. One of the notable changes in aggressive cancers is that the E-cadherin is down-regulated, while N-cadherin up-regulated. As an important mesenchymal marker, N-cadherin is a transmembrane protein that interacts with other cadherins at the extracellular domain and catenins at the intracellular domain. Previous studies have found N-cadherin overexpression to promote the motility of several cancer cell lines. Additionally, our research has shown that invasive cells in a three-dimensional matrix often migrate collectively using N-cadherins. Through the interaction with catenins, N-cadherins, in principle, are able to regulate the actin filament network and thus, cell migration. To understand the role of N-cadherin in collective cell migration, we designed cell traction force experiments to analyze the forces that are transmitted through N-cadherin bonds. Using N-cadherin mutants with altered cytoplasmic domains and purified N-cadherin-coated, force-sensing substrates, we show that the cytoplasmic domain of N-cadherin is essential for the efficient transmission of traction forces. One of the mutants we generated was a N-cadherin mutant with an actin binding site. Interestingly, the expression of this mutant resulted in decrease in traction force, while increase in cell migration on the N-cadherin-coated surface. Our results demonstrate that N-cadherin interactions are sufficient for cells to transmit forces and migrate along N-cadherin surface, and provide an explanation for the presence of N-cadherin in aggressive cancer cells.

DEVELOPMENT OF QUANTITATIVE METHODS FOR ASSESSING METASTATIC POTENTIAL OF HUMAN PRIMARY TUMORS

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The inability to effectively treat metastases is the main reason for the limited progress in reducing the rates of cancer morbidity and mortality. One major drawback is the lack of quantitative assays for assessing the size and tissue prevalence of tumors in newly diagnosed individuals. Current methods for quantifying tumor burden are mainly qualitative and include measuring the gross weight of the affected organ, counting tumors on the surface of the organ, or evaluating a small sample of the organ using histologic sections. These methods are crude measures of tumor burden and size distribution, and in the case of histology, they are time consuming, difficult to process an adequate sample size and non-quantitative. Animal models of metastasis have been useful in identifying genes that regulate susceptibility to the development and progression of metastasis and helped highlight potential novel targets for drug development. In particular several small animal imaging technologies including magnetic resonance imaging, high frequency ultrasound, and optical imaging have been recently applied to this task. Each of these methods may be useful for specific research projects, based on their unique combination of resolution, image acquisition time, animal throughput, and cost-effectiveness, yet none of these modalities adequately address the need for rapid quantification of tumors across the entire organism, nor do they assess therapeutic effectiveness in eradicating cancer in xenograft models. We have developed an Accelerator Mass Spectrometry-based high precision quantitative method for assessing the metastatic potential of primary tumors isolated from newly diagnosed patients. This system uses xenograft cancer cells labeled with $^{14}$C-labeled thymidine ($C14TdR$) that are delivered intravenously into NSG mice and allowed to develop metastatic cancer over the course of 10 weeks. At the end of the experiment, all vital organs are collected; the DNA is isolated and is
examined by AMS for the presence of $^{14}$C-signal. The labeling was optimized to achieve sufficient signal such that a tumor derived from a single cell could be detected by AMS, in secondary tumors, \textit{in vivo}, independent of histological data. Using this approach we have evaluated the metastatic potential of several prostate cancer cell lines, characterized stem-cell like sublines derived from PC3 cells and examined tissue tropism of cancer sublines derived from kidney and liver metastatic tumors. Further optimization of these techniques will allow us to explore the metastatic potential of primary tumors, isolated from biopsies and expanded in Avatar mice.

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<<11>> TRENDS IN COLORECTAL CANCER IN CALIFORNIA: ARE WE FAILING HISPANIC MEN?

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Background: Colorectal cancer (CRC) incidence and mortality have decreased dramatically since 1990 due primarily to increased screening. However, CRC incidence and mortality have not decreased among Hispanic males in California. We examine trends in incidence, mortality and survival to explore whether the effects of screening and access to healthcare could explain differential trends between Hispanics and non-Hispanic white men.

Methods: We used California Cancer Registry (CCR) data to identify Hispanic and non-Hispanic white men diagnosed with CRC between 1990 and 2011. We examined trends in mortality and incidence stratified by age and stage and trends in the proportion of tumors by stage and location within the colon and rectum.

Results: Although incidence was substantially higher among white than Hispanics in 1990, by 2011 rates were comparable between the two groups. Similar trends were seen in mortality. White men had greater improvement in incidence and mortality among all age groups. Hispanic men had a higher proportion of tumors in the distal colon.

Conclusion: While CRC incidence and mortality in California have decreased among white men since 1990 they have remained flat among Hispanic men. Possible reasons for the discrepancies include lack of screening and lack of access to healthcare.

<<12>> PROSPECTIVE EVALUATION OF INTRA AND INTERFRACTION CERVICAL MOTION DURING EXTERNAL BEAM RADIATION FOR INTACT CERVICAL CANCER USING AN ELECTROMAGNETIC TRACKING SYSTEM

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Introduction: Accurate assessment of cervical motion is critical to optimize definitive radiotherapy target volumes. We report a prospective, multi-institutional feasibility study evaluating implementation of an electromagnetic tracking system (EM) in concert with daily cone beam computed tomography (CBCT) to investigate cervical inter- and intra-fraction motion.

Methods: Cervical cancer patients undergoing definitive radiation were prospectively enrolled at 2 institutions. Prior to simulation, EM transponders were placed in the cervix directly or embedded in a Smit sleeve. Daily CBCT registered to pelvic bony anatomy was used to evaluate the location
and any migration of the transponders. The interfraction EM isocenter, and cervical intrafraction motion were recorded and analyzed with descriptive statistics and analysis of variance (ANOVA).

Results: Twelve patients were enrolled, with 10 complete data records for evaluation. FIGO stage was 1B1-3B, with a mean age of 52 years (range 30-68), and included nine (90%) squamous carcinoma and 1 (10%) adenocarcinoma. Nine (90%) underwent concurrent cisplatin chemotherapy. During the course of treatment, 1 of 5 patients experienced loss of transponders placed on the smit sleeve. In 5 patients the transponders were directly implanted into the cervix, and due to loss, 2 (40%) required additional transponder placement. 200 daily CBCT images were obtained and aligned to pelvic bony anatomy with the following positional data shifts $(x_{\text{mean}}, x_{\text{range}}; y_{\text{mean}}, y_{\text{range}}; z_{\text{mean}}, z_{\text{range}})$ in average and range positions in cm: (-0.01, -1.6-3.4; 0.05, -3.8-1.9; -0.49, -9-5.1). For the 4 patients for whom motion data is available for analysis, there were more than 6000 position measurements per patient. Over the treatment course, the maximum displacement in cm $(x, y, z)$ of the EM isocenter from day 1 are (.48, .86, 2.5); (.74, 1.05, .88); (.81, 1.9, 1); (.35, .53, .37), respectively for the 4 patients. The maximum and mean excursions over the treatment course in cm are left (.34, .06) right (.32, .03) sup (.27, .08) inferior (1.27, .08) anterior (.72, .09) post (.32, .08). There was no statistically significant differences between directional excursions, with a trend for a higher inferior maximal excursion, $p<0.1825$. Patients had a significant difference in the daily EM isocenter during the treatment course comparing subsequent treatments to day 1, $p<0.001$.

Conclusions: Using EM implanted transponders to study intact cervical motion for target margin optimization is feasible, but may require additional transponder placements due to loss, migration and tumor shrinkage. Intrafraction motion of the cervix demonstrates a greater maximal excursion in the inferior direction, >1cm. This interfraction motion during the course of therapy justifies the use of daily image guidance to ensure adequate target coverage.

<<13>> BIOPHYSICAL CHARACTERIZATION OF A RAD51 MUTATION THAT CAUSES A FANCONI ANEMIALIKE DISORDER

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RAD51 is a DNA-dependent ATPase involved in double-strand break repair and maintenance of replication forks that encounter DNA lesions. A patient with a Fanconi Anemia (FA)like disorder was recently found to have no mutations in known FA genes, but had a single point mutation in one copy of RAD51 (T131P). A previous study showed that this RAD51 mutation causes DNA repair defects \textit{in vivo} and has severely impaired biochemical activity \textit{in vitro}. Interestingly, T131P showed DNA-independent ATPase activity. In the current study, traditional and single-molecule assays revealed that this RAD51 mutant loses DNA binding activity at 37°C, but not ATPase activity. Atomic force microscopy revealed that T131P has a larger oligomer size after incubation at 37°C, suggesting that enhanced oligomerization of T131P leads to a loss of DNA-binding activity while allowing DNA-independent ATPase activity. Since the patient is heterozygous, current work is aimed at identifying the activity of mixtures of WT and T131P protein.
SUBLOBAR RESECTION AND VIDEO-ASSISTED THORACIC SURGERY APPROACH ARE ASSOCIATED WITH DECREASED POSTOPERATIVE ATRIAL FIBRILLATION/FLUTTER AFTER LUNG CANCER SURGERY—A NATIONWIDE INPATIENT SAMPLE ANALYSIS

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OBJECTIVES: Previous reports show that postoperative atrial fibrillation and flutter (POAF) increases 30-day mortality after surgery for non-small cell lung cancer (NSCLC). Non-definitive data in prior studies characterizing the incidence of POAF after minimally invasive thoracic surgery may be a result of limited study populations and small sample size. Using a large cohort, we hypothesized that: 1) sublobar resection is associated with a decreased risk of POAF compared to lobectomy for NSCLC, and 2) video-assisted thoracic surgery (VATS) is associated with a decreased risk of POAF compared to thoracotomy (OPEN).

METHODS: This is a retrospective cohort study, using the Healthcare and Utilization Project Nationwide Inpatient Sample (HCUP-NIS) database from 2008 to 2011. ICD-9-CM codes were used to identify adult patients who underwent elective lobectomy, segmentectomy or wedge, via OPEN or VATS for primary NSCLC. Patients with unknown discharge disposition were excluded. We determined the incidence of POAF and its effects on both mortality and discharge disposition (home or institutionalized care facility [ICF]). Multivariable logistic regression models, including age, sex, co-morbidities, OPEN versus VATS, and extent of lung resection were used to identify independent predictors of POAF. A \(p\) value \(\leq 0.05\) was significant.

RESULTS: The cohort included 28,314 patients (53.1% women). Table 1A shows the types of resections done. The overall incidence of POAF was 17.7% (n=5,008) and Table 1B shows the incidence of POAF for each resection type. Patients who developed POAF had increased mortality (3.3% vs. 1.3%, \(p<0.01\)), and were more likely to be discharged to an ICF than those who did not (\(p<0.01\)). Congestive heart failure (CHF; OR 2.6, 95% CI 2.3-3.0) and cerebrovascular disease (CVD; OR 2.1, 95% CI 1.4-2.9) were the strongest independent predictors of POAF. In multivariable analyses, POAF was 35% (OR 0.7, 95% CI 0.6-0.7) less common in sublobar resections and 28% (OR 0.7, 95% CI 0.7-0.8) less common with VATS. When compared to OPEN segmentectomy, VATS lobectomy had a decreased risk of POAF (19.3% vs. 16.9%, \(p<0.04\)).

CONCLUSIONS: Patients undergoing sublobar resection for NSCLC have a decreased risk of POAF. Our analyses also suggest that a VATS approach decreases the risk of POAF. Those with POAF are at increased risk of discharge to ICF and death. Patients at greatest risk of POAF, including those with CHF and/or CVD requiring lobectomy or thoracotomy, may benefit from more intensive prophylactic measures.

| Table 1B. Incidence of POAF after lung resection via OPEN or VATS |
|------------------|------------------|------------------|
| OPEN POAF | VATS POAF | \(p\) value |
| Lobectomy | 20.2% (n=2,638) | 16.9% (n=939) | \(p<0.01\) |
| Segmentectomy | 19.3% (n=246) | 14.6% (n=172) | \(p<0.01\) |
| Wedge | 15.8% (n=438) | 12.9% (n=575) | \(p<0.01\) |

NSCLC=non-small cell lung cancer; POAF=postoperative atrial fibrillation and flutter; VATS=video-assisted thoracic surgery
TARGETED DEPLETION OF CHEMOTHERAPY RESISTANT BREAST CANCER CELLS BY INDUCTION OF A LYSOSOME AND REACTIVE OXYGEN SPECIES DEPENDENT PROGRAMMED CELL DEATH

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Therapeutic resistance leading to tumor recurrence is a major clinical barrier in breast cancer treatment. Accumulating evidence suggests cancer stem cells (CSC), characterized by their capacity for self-renewal and generation of heterogeneous progeny, are essential to tumor recurrence following therapy and development of metastatic lesions. As such, directed targeting of CSC provides a rational approach to overcoming tumor recurrence and therapeutic resistance to improve patient outcomes. Our unpublished studies suggest the amiloride derivative, UCD19 as a strong candidate for the depletion of therapy resistant breast cancer cells. In particular, UCD19 reduced the viability of breast cancer cells but not nontransformed cells in vitro irrespective of their molecular profile (hormone/growth factor receptor status, p53 expression), species type (mouse, human) or proliferative status. The cell death curves of UCD19 in breast cancer cells were steep, reflecting a complex mechanism underling its cytotoxicity. Along these lines, we established that UCD19 induced a novel form of programmed necrosis (type III programmed cell death (PCD)) relying on the orchestration of mitochondrial and lysosomal derived prodeath factors. We determined that UCD19 induced the hallmarks of type III PCD (loss of plasma membrane integrity without nuclear condensation), perturbed lysosomal dynamics and significantly affected mitochondrial structure. Moreover, UCD19 promoted an increase in the production of reactive oxygen species (ROS) and a reduction in prosurvival factors (protein kinase B (PKB)/Akt and extracellular regulated kinase (ERK)). Using fluorescence activated cell sorting and tumor stem cell assays, we demonstrate that unlike the standard chemotherapeutic docetaxel, UCD19 is capable of markedly depleting CSC. These data suggest that UCD19 is particularly well suited for investigation into novel mechanisms of programmed necrosis, for understanding means by which we can target CSC populations, and potential as a potential therapeutic for the ablation of chemotherapy- and apoptosis-resistant breast cancers.

PHYSIOLOGICAL ROLE OF BRCA2-SYCP3 INTERACTION DURING MEIOTIC RECOMBINATION.

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Homologous recombination occurs when a broken or damaged chromosome uses matching sequences on a second intact chromosome as a template for repair synthesis. In somatic cells, defective recombination causes genome instability, a characteristic of many cancers. Thus, recombination is a major tumor suppressor pathway. Recombination is also essential for reproduction. Defective meiotic recombination causes de novo mutations and aneuploidy that can lead to pregnancy miscarriages and common chromosomal diseases such as Down Syndrome.

BRCA2 (Breast Cancer Associated) gene is an essential recombination factor. In somatic cells, BRCA2 functions in the central step of recombination by facilitating the assembly of RAD51 at sites of DNA lesions. In somatic cells, mutations in BRCA2 cause genomic instability and underlie a large fraction of hereditary breast cancers. A novel mechanism of inhibiting BRCA2 function in cancer cells was recently suggested by the observation that SYCP3, a cancer testis antigen whose expression is normally confined to meiosis, interacts with BRCA2.

In meiosis, SYCP3 localizes along the lengths of the chromosomes where it facilitates the organization of meiotic chromatin and regulates various aspects of recombination. The precise
function of BRCA2 and the physiological role BRCA2-SYCP3 interaction in meiotic recombination remains outstanding questions in developmental biology. For the first time using two independent antibodies, we have optimized BRCA2 immunostaining to reveal a punctate pattern of foci that are specifically localized along the SYCP3-staining chromosome axes. Unlike other recombination factors, such as RAD51, BRCA2 foci are detected throughout meiotic prophase, but always in association with SYCP3. Moreover BRCA2 foci form independently of chromosome synapsis (in synopsis-defective Sycp1−/−mice); and, unexpectedly, do not require the presence of DNA damage as foci are still detected in the Spo11 mutant, which lacks DNA double-strand breaks. However BRCA2 is not detected along the chromosome axes of Sycp3 mutants consistent with a physical and functional interaction between these two proteins. Further understanding of the physiological role of BRCA2-SYCP3 interaction will provide insights both into the mechanism and regulation of meiotic recombination, and how SYCP3 contributes to tumorigenesis.

**SOST INHIBITS PROSTATE CANCER INVASION BY REPRESSING LONG NONCODING RNA MALAT1**

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Dynamic interaction between prostate cancer and the bone microenvironment is a major contributor to metastasis of prostate cancer to bone. Inhibitors of Wnt signaling have been shown to be involved in prostate cancer (PC) metastasis; however the role of Sclerostin (Sost) has not yet been explored. Previously, we have shown that elevated Wnt signaling derived from Sost deficient osteoblasts promotes PC invasion, while rhSOST has an inhibitory effect. In contrast, rhDKK1 promotes PC elongation and filopodia formation, morphological changes characteristic of an invasive phenotype. Furthermore, rhDKK1 was found to activate canonical Wnt signaling in PC3 cells, suggesting that SOST and DKK1 have opposing roles on Wnt signaling in this context. Furthermore, we investigated the effects of high concentrations of SOST in vivo and found that PC3-cells overexpressing SOST injected via the tail vein in NSG mice did not readily metastasize, and those injected intrafemorally had significantly reduced osteolysis, suggesting that targeting the molecular bone environment may influence bone metastatic prognosis in clinical settings. We also examined molecular changes in an in-vitro co-culture model of PC3 prostate cancer cells and osteoblasts followed by microarray based gene expression profiling to identify previously unrecognized prostate cancer-bone microenvironment interactions. Factors secreted by PC3 cells resulted in the up-regulation of many genes in osteoblasts associated with bone metabolism and cancer metastasis, including Mmp13, Il-6 and Tgfb2, and down-regulation of Wnt inhibitor Sost. To determine whether altered Sost expression in the bone microenvironment has an effect on prostate cancer metastasis, we co-cultured PC3 cells with SostKO osteoblasts and wildtype (WT) osteoblasts and identified several genes differentially regulated between PC3-SostKO osteoblast co-cultures and PC3-WT osteoblast co-cultures. Co-culturing PC3 cells with WT osteoblasts up-regulated cancer-associated long noncoding RNA MALAT1 in PC3 cells. MALAT1 expression was further enhanced when PC3 cells were co-cultured with SostKO osteoblasts and treatment with recombinant Sost down-regulated MALAT1 expression in these cells. Our results suggest that reduced Sost expression in the tumor microenvironment may promote bone metastasis by up-regulating MALAT1 in prostate cancer.
CTEN REGULATES RECEPTOR TYROSINE KINASES IN CANCER CELLS

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Cten, a member of the tensin family protein, localizes at focal adhesion sites. Its PTB domain binds to the integrin β1 tail, while SH2 domain interacts with many proteins such as DLC1, a tumor suppressor, and c-Cbl, an E3 ubiquitin ligase. It is recently emerging as a putative oncogene in many types of cancers. Our lab has shown that cten prolongs EGFR signaling through inhibition of the ubiquitination of EGFR by c-Cbl and further preventing EGFR from the degradation (1). c-Cbl ligase activity is switched on by phosphorylation of its tyrosine residue (2). Cten has also been shown stabilizing Met through direct interaction in carcinoma cells (3). We found that in Hela cells knockdown of cten significantly prompts a reduction of platelet-derived growth factor receptor β (PDGFRβ). The degradation of PDGFRβ through the ubiquitination by c-Cbl has been well studied (4). We hypothesize that cten positively regulates PDGFRβ either through direct interaction or through the interaction with c-Cbl. Here we showed that in Hela cells cten knockdown induces an increase in c-Cbl tyrosine-phosphorylation level, implying ligase activity increases. The level of ubiquitinated PDGFRβ will be examined. The relationship among cten, c-Cbl and PDGFRβ, as well as their binding domains will be investigated. Different cancer cell lines will be tested to validate these results.

References:

OVERCOMING EGFR-INDUCED RESISTANCE TO ENZALUTAMIDE IN CASTRATION RESISTANT PROSTATE CANCER

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Background: The androgen receptor (AR) remains a major therapeutic target in patients with castration-resistant prostate cancer (CRPC). Enzalutamide, an AR inhibitor that is FDA-approved for patients with CRPC, prevents ligand induced AR transcriptional activity, but some initial responders eventually become resistant to the drug. The expression and activity of the EGFR/ErbB family of receptor tyrosine kinases also increases in CRPC patients. The present work was undertaken to determine whether the activation of EGFR family (EGFR/ErbB2/ErbB3/ErbB4) may be responsible for enzalutamide resistance and whether treatment with receptor tyrosine kinase inhibitors would overcome this effect.

Methods: Human-patient-derived androgen-dependent and CRPC prostate tumor cells were grown in 10% Fetal Bovine Serum (FBS). Protein expression and phosphorylation status of the EGFR family were determined by immunoblotting techniques. MTT assays were used to determine the viability of cells treated with enzalutamide, lapatinib (HER2/EGFR inhibitor), erlotinib (EGFR inhibitor), or dacomitinib (pan-ErbB inhibitor). A Luciferase Assay kit (Roche) was used to determine AR transcriptional activity. Lapatinib was obtained from LC Laboratories while erlotinib and dacomitinib were obtained from Selleck Chemicals. Enzalutamide was kindly provided by Medivation Inc.
Results: In viability assays, erlotinib and dacomitinib, but not lapatinib, sensitized CRPC cells to enzalutamide. Enzalutamide suppressed AR transcriptional activity, either alone or in combination with lapatinib, erlotinib, or dacomitinib. Erlotinib, lapatinib, and dacomitinib equally inhibited EGFR and ErbB3 phosphorylation. However, in EGF stimulated cells, erlotinib and dacomitinib—but not lapatinib—suppressed ERK 1/2 phosphorylation at Tyr202/Thr204, indicating a stark difference in downstream inhibition and potentially proliferation.

Conclusions: The above results indicate that ERK 1/2 may play an important role in reducing the efficacy of the enzalutamide and lapatinib combination. Furthermore, lapatinib’s inability to prevent ERK phosphorylation upon EGF stimulation likely plays a role in its ineffectiveness in prostate cancer. Our preliminary preclinical data indicate that co-administration of enzalutamide with an EGFR targeted inhibitor may be a suitable therapeutic approach towards overcoming enzalutamide resistance in vitro. This strategy may potentially prolong enzalutamide sensitivity in CRPC patients.

GENETICALLY ENGINEERED MIR-34APRODRUG SUPPRESSES ORTHOTOPIC OSTEOSARCOMA TUMOR GROWTH VIA THE INDUCTION OF APOPTOSIS AND CELL CYCLE ARREST

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Background: Osteosarcoma (OS) is the most common primary malignant bone tumor in children and young adults and microRNA-34a (miR-34a) represents a new agent to treat cancer diseases. Recently we have developed a novel approach to bioengineering miR-34a prodrug. This study is to define the effectiveness and safety profiles of biological miR-34a prodrug in an orthotopic OS xenograft tumor mouse model.

Methods: MTT assay was used to examine antiproliferative activity against OS cells, and Matrigel invasion assay was employed to determine invasion capacity. Impact of miR-34a on apoptosis and cell cycle were assessed by cytometric studies, and protein levels of several miR-34a target genes were evaluated by Western blots. Orthotopic 143B xenograft mouse model was established to define the efficacy of miR-34a prodrug formulated with in vivo-jet PEI and administered intravenously. Blood chemistry profiles were determined to assess safety profiles.

Results: Biologic miR-34a prodrug significantly reduced the proliferation of human OS143B and MG-63 cells in a dose dependent manner and to a much greater degree than the controls, which was attributable to the induction of apoptosis and G2 cell cycle arrest. Inhibition of cell growth and invasion were associated with reduction of protein levels of miR-34a target genes including SIRT1, BCL2, c-MET, and CDK6. Furthermore, therapeutic doses of miR-34a prodrug significantly repressed the growth of orthotopic 143B xenograft tumors and were well tolerated in the animals.

Conclusions: Bioengineered miR-34a prodrug is effective to control OS tumor growth which involves the induction of apoptosis and cell cycle arrest.
MICRORNA-1291 SUPPRESSES PANCREATIC TUMORIGENESIS THROUGH THE REGULATION OF FOXA2-AGR2 PATHWAYS

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Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in the United States. Despite extensive investigation, PDAC remains a lethal cancer disease with poor prognosis because of the metastatic nature, lack of diagnostic markers, and a low efficiency of current treatment. MicroRNAs (miRs or miRNAs) are critical factors in the control of tumor initiation and progression via regulating the expression of cancer-related genes. Our recent studies have showed that snoRNA-derived miR-1291 regulates efflux transporter ABCC1/MRP1 and alters the metabolome of pancreatic carcinoma cells. This study was to investigate the role and molecular mechanisms of miR-1291 in the suppression of pancreatic tumorigenesis. Stable miR-1291 expressing PANC-1 and AsPC-1 cells were established, which both showed a significantly lower rate of proliferation and tumorigenesis than the control cells. Proteomic studies revealed the change in protein levels of a set of cancer-related genes by miR-1291, among which the pancreatic tumor marker AGR2 was reduced about 10-fold in miR-1291-expressing cells. Through computational and experimental studies we further identified that FOXA2, a direct regulator of AGR2, was a direct target of miR-1291. Indeed, miR-1291-expressing cells had significantly lower levels of FOXA2 and AGR2. In addition, we demonstrated an overexpression of AGR2 and down-regulation of miR-1291 in PDAC patient tumor samples. These results suggest that suppression of pancreatic tumorigenesis by miR-1291 may involve miR-1291-FOXA2-AGR regulatory pathways, which would provide new insights into developing miR-1291-based therapy for PDAC.

MIRNA-DEPENDENT REGULATION OF TUMOR SUPPRESSOR LRIG1 IN BREAST CANCER

Maxine Umeh, Sumaira Amir, Colleen A. Sweeney

LRIG1 has been established by the Sweeney lab as a tumor suppressor involved in the regulation of human breast cancer. LRIG1 negatively regulates the expression of multiple receptor tyrosine kinases, most notably the ERBB family of receptors, which promote cell growth, proliferation, and survival. LRIG1 is significantly down regulated, or completely lost, in most breast cancers, however how this down regulation occurs is not fully understood. In fact, overall regulation of LRIG1 is poorly understood. This project seeks to investigate LRIG1 regulation in breast cancer. One such mechanism is through microRNAs. We have identified LRIG1 as a target of miR-106b. Down regulation of LRIG1 by miR-106b results in hyper-activation of the MAP kinase pathway resulting in increased cell growth and survival. In addition to being a direct target of miR-106b, LRIG1 may also be regulated by a larger network of competing endogenous RNA (ceRNAs). ceRNAs are mRNAs which are targeted by a shared group of microRNAs, “competing” for interactions with these miRNAs, and thus regulating one another’s expression. LRIG1 is a ceRNA to multiple tumor suppressors: PTEN, ERBB2IP, TP53INP1, PIK3R1, and RBL2. We hypothesize that expression of these ceRNAs regulates expression of LRIG1. Loss of these ceRNAs leads to lowered expression of LRIG1, while their overexpression increases LRIG1 levels. We hypothesize that this mechanism can be exploited to significantly increase LRIG1 levels in breast cancer cells and thus inhibit cancer onset and/or progression. We hope to establish LRIG1, and its ceRNAs, as potential therapeutic targets in breast cancer.
**A LONG NONCODING RNA CONNECTS C-MYC TO TUMOR METABOLISM**

Chiu-Lien Hung, Ling-Yu Wang, Yen-Ling Yu, Hongwu Chen, Shiv Srivastava, Gyorgy Petrovics, Hsing-Jien Kung

Long non-coding RNAs have been implicated in a variety of physiological and pathological processes including cancer. In prostate cancer, PCGEM1 (prostate cancer gene expression marker 1) is an androgen-induced prostate specific lncRNA whose overexpression is highly associated with prostate tumors. PCGEM1's tumorigenic potential was recently shown to be in part due to its ability to activate androgen receptor (AR). Here we report a novel function of PCGEM1 that provides growth advantages for cancer cell by regulating tumor metabolism via c-Myc activation. PCGEM1 promotes glucose uptake for aerobic glycolysis, coupling with pentose phosphate shunt to facilitate biosynthesis of nucleotide and lipid, and generates NADPH for redox homeostasis. We show that PCGEM1 regulates metabolism at the transcriptional level that affects multiple metabolic pathways including glucose and glutamine metabolism, pentose phosphate pathway, nucleotide and fatty acid biosynthesis, and TCA cycle. The PCGEM1-mediated gene regulation takes place in part through AR activation, but predominantly through c-Myc activation regardless of hormone or AR status. Significantly, PCGEM1 binds directly to target promoters, physically interacts with c-Myc, promotes chromatin recruitment of c-Myc, and enhances its transactivation activity. We also identified c-Myc binding domain on PCGEM1 that contributes to the PCGEM1 dependent c-Myc activation and target induction. Together, our data uncover PCGEM1 as a key transcriptional regulator of central metabolic pathways in prostate cancer cell. By being a coactivator for both c-Myc and AR, PCGEM1 reprograms the androgen network and the central metabolism in a tumor specific way, making it a promising target for therapeutic intervention.

**COMBINED METABOLOMICS AND PROTEOMICS TO UNCOVER METABOLIC REPROGRAMMING IN KIDNEY CANCER**

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Division of Nephrology and Cancer Center, UC Davis; Medical and Research Services, VA Medical Center, Mather, CA;

Rationale: Kidney cancer (or renal cell carcinoma; RCC) is known as “the internist’s tumor” because it has protean systemic manifestations which suggest that it utilizes complex, non-physiologic metabolic pathways. Given the increasing incidence of this cancer and its lack of effective therapeutic targets, we hypothesized that RCC undergoes extensive metabolic reprogramming to evade conventional chemotherapy. We undertook an extensive analysis of human RCC tissue employing combined grade-dependent proteomics and metabolomics analysis in order to determine the nature of the metabolic reprogramming occurring in this disease that allows it to successfully escape most current as well as classical therapeutic measures

Methods: Non-targeted metabolomics (n = 187) and proteomics (n = 40) were performed in human RCC tissues as a function of pathological Fuhrman grade with adjacent “normal” tissues as controls. Energy relevant as well as tryptophan metabolic pathways were compared and both omics data were hand curated. All pathway data were validated in cell culture systems.

Results: (Figure) We showed that the Warburg effect is prominent in RCC at higher grade, at the expense of the tricarboxylic acid cycle and oxidative metabolism in general. In addition, the
glutamine metabolism pathway is directed towards reactive oxygen species inhibition, as is evidenced by an upregulated glutathione pathway, while the β-oxidation pathway is inhibited leading to increased fatty acyl-carnitines. Consistent with our previous human urine metabolomics data, we show here that the metabolism of tryptophan to anti-inflammatory metabolites, rather than other metabolic pathways, is highly represented in RCC.

**Conclusions:** RCC undergoes extensive metabolic reprogramming which allows it to escape conventional as well as current targeted therapies. Many of these new pathways are amenable to novel therapies and can be rapidly translated to the clinic. A similar approach can be taken in other cancers.

**MOLECULAR PHARMACOLOGY SHARED RESOURCE (MPSR) SUPPORT OF UC DAVIS COMPREHENSIVE CANCER CENTER CLINICAL RESEARCH**

Leslie Solis¹, Rebekah Tsai¹, Yu Li¹, Frank Sierra¹, Danh Nguyen¹, and Philip Mack¹,²

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As the demand for more sensitive and accurate biomarkers with predictive or prognostic utility grows, so does the need for integrating basic research, high-quality biospecimen collection, and the development of strong collaborations between academic researchers and industry.

The Molecular Pharmacology Shared Resource (MPSR) serves as a single point of contact for UC Davis Comprehensive Cancer Center-associated researchers interested in developing and testing novel agents and biomarkers in the clinical trials setting. Our services support a *bench-to-bedside-to-bench* approach to clinical translational research, from concept development via preclinical therapeutic modeling, assay development, protocol design, biospecimen collection and storage, correlative investigations of patient samples, and data analysis.

Preclinical modeling carried out by the MPSR includes both *in vitro* studies of novel anticancer regimens as well as a productive collaboration with The Jackson Laboratory (JAX) to conduct studies in patient-derived xenografts (PDXs). Clinically, the MPSR works in collaboration with the Office of Clinical Research (OCR) to support an average of 150 clinical trials annually, including the development of specimen collection procedures, clinical trial protocol language, the collection and processing of over 3000 patient specimens annually and the release of specimens to protocol-defined researchers. Our facilities utilize a customized specimen-tracking software package (Freezerworks Unlimited) to securely record and track all pertinent information on each specimen. This software meets all state and federal standards for health information databases, including 21 CFR Part 11 and HIPAA, and allows us to provide detailed, timely and accurate specimen reports. For UCDCC researchers, the MPSR also manages and conducts correlative analysis of clinical trial specimens, closing the loop on the trial and helping to define a framework for further investigation.

Overall, the MPSR achieves its goals of providing user-friendly translational support for clinical trials at UCDCCC, with assistance to researchers at all steps of protocol development, from initial conception to final publication. The MPSR manages all of your clinical trials blood specimens from collection to analysis, and is highly responsive to all investigator and sponsor needs. Our close collaborations with outside researchers, industry, and within the UCDCCC provide a unique opportunity to carry out a wide range of correlative research, ranging from small phase I investigator-initiated studies to large, randomized phase III trials.
A CLUSTER RANDOMIZED CONTROLLED TRIAL OF A LAY HEALTH WORKER INTERVENTION TO PROMOTE COLORECTAL CANCER SCREENING AMONG HMONG AMERICANS

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Background: Colorectal cancer (CRC) is one of the most common cancers in the U.S. and is preventable by screening for early detection, yet CRC screening rates are suboptimal for most population groups, including Asian Americans and immigrants.

Methods: From 2012-2015, using a community-based participatory research (CBPR) approach, we conducted a cluster randomized controlled trial to evaluate the effect of a lay health worker (LHW) intervention on CRC screening among Hmong Americans aged 50 to 75 in Sacramento, CA. Each LHW was asked to recruit 12-15 participants. After recruitment, LHWs and their participants were randomly assigned to the CRC intervention group or a nutrition-physical activity control group. CRC intervention participants received 2 LHW-delivered educational group sessions, 2 LHW follow-up telephone calls, and a brochure about CRC and its prevention. Control group participants received 2 health educator-delivered lectures and 2 follow-up telephone calls about nutrition and physical activity, and the CRC brochure. All study materials were in Hmong or English. All participants answered a pre-intervention survey immediately prior to the first education session or lecture and a post-intervention survey 6 months later. Multivariable logistic regression models were used to examine intervention effects on self-reported receipt of any CRC screening (fecal occult blood test [FOBT], sigmoidoscopy, or colonoscopy) ever, and being up-to-date with CRC screening (FOBT within 1 year, sigmoidoscopy within 5 years or colonoscopy within 10 years). All analyses accounted for clustering of participants by LHW using generalized estimating equations (GEE).

Results: Hmong Women’s Heritage Association recruited and trained 29 LHWs age 21-55, 83% of whom were women. The LHWs recruited 329 participants (74% women, 65% married, 100% foreign-born, 71% speaking English poorly or not at all, 90% with no formal education, 54% with income < $20,000/year, and 94% with a regular place of healthcare). At baseline, 68% had ever had an FOBT and 22% a sigmoidoscopy or colonoscopy. The 6-month participant retention rate was 98%. There were significant increases in receipt of any CRC screening ever in the intervention group (72% to 83%, p=0.0001) but not in the control group (71% to 75%, p=0.21), with the intervention group change significantly greater than the control group change (p=0.037). The proportion who were up-to-date with CRC screening also increased significantly in the intervention group (44% to 58%, p<0.0001) but not in the control group (43% to 44%, p=0.71), with the intervention group change greater than the control group change (p<0.0001). Multivariable models adjusting for sociodemographic variables showed that the intervention was effective in increasing both ever screening (OR=1.7, 95% CI 1.0-2.7, p=0.037) and up-to-date screening (OR=1.8, 95% CI 1.3-2.4, p=0.0004).

Conclusion: LHWs effectively increased CRC screening among older Hmong Americans. Findings illustrate the benefits of CBPR in yielding high research participant retention by partnering with trusted community leaders in seemingly hard-to-reach communities such as these older Hmong immigrants with little formal education and limited English proficiency.

This was funded by NCI to AANCART
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## Call for suggested speakers:

*Call for suggested speakers:

A message from Dr. Kermit Carraway III, Cancer Biology Seminar Series Coordinator

With the aim of continuing the level of excellent talks, I am seeking nominations for invited speakers for the CBS series for the Spring quarter, early March through early June, 2016. Invited speakers may represent any academic institution or industry in North America, and should have expertise in molecular, cellular, genetic/genomic, viral, pharmacological or immunological aspects of cancer biology. Nominations of speakers interested in related disciplines such as developmental biology, pathology, genomics, imaging technology, etc. are also welcome; priority will be given to speakers whose work connects directly with cancer.

Faculty, this is a terrific opportunity to meet scientists whose work you admire, or to initiate or cement collaborative interactions.

Grad students, post-docs and other trainees, I strongly encourage you to contribute to the seminar series by nominating speakers who you feel would be particularly interesting, or who might be a useful contact for you in the future.

Please forward the names, institutional affiliations and any available contact information to me (kcarraway@ucdavis.edu) before November 6, 2015.

Thank you!