INNOVATIONS
In Cancer Prevention and Research Conference

PROGRAM & ABSTRACTS

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CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

NOVEMBER 13-14
2017
RENAISSANCE HOTEL
AUSTIN, TEXAS
# Program Guide

About CPRIT ................................................................. 2
CPRIT Oversight Committee and Executive Team .......................... 3

**Schedule At A Glance** .................................................. 4
  MONDAY, NOVEMBER 13 ................................................. 5
  TUESDAY, NOVEMBER 14 ................................................. 6

**Detailed Session Descriptions and Speaker Information** ............. 8
  MONDAY, NOVEMBER 13 ................................................ 14
  TUESDAY, NOVEMBER 14 ................................................ 14

Renaissance Hotel Floor Plan ............................................. 26
Austin Arboretum Map .................................................... 27

## Abstracts

### Academic Research

- Cancer Biology (Abstracts 1–120) ..................................... 29
- CPRIT Core Facility (Abstracts 121 through 156) .................. 60
- Etiology/Early Detection/Diagnosis (Abstracts 157 through 197) .. 70
- Prevention/Cancer Control and Survivorship (Abstracts 198 through 229) ............... 81
- Treatment/Therapeutics (Abstracts 230 through 296, 420 and 421) .................. 90

### Product Development Research

- Detection and Diagnostics (Abstracts 297–307) .................... 109
- Treatments and Therapeutics (Abstracts 308–335) .................. 112

### Prevention

- Primary Prevention (Abstracts 336 through 363) .................. 119
- Early Detection and Screening (Abstracts 364 through 410) .......... 127
- Survivorship (Abstracts 411 through 419) .......................... 140
ABOUT CPRIT

Texas voters overwhelmingly approved a constitutional amendment in 2007 establishing the Cancer Prevention and Research Institute of Texas and authorizing the state to issue $3 billion in bonds to fund groundbreaking cancer research and prevention programs and services in Texas. CPRIT’s goal is to expedite innovation in cancer research and product development, and to enhance access to evidence-based prevention programs throughout the state.

CPRIT’s objective is to position Texas as a world-class leader in research and prevention through collaboration with a variety of entities, including public and private institutions of higher education, governmental and nongovernmental organizations, and private companies and others involved in the fight against cancer. CPRIT supports innovation in the selection of research projects emphasizing immediate or long-term medical breakthroughs; product development translational opportunities for research, and prevention services and health education for citizens with culturally appropriate information about ways in which their risks of developing and dying from cancer can be reduced. CPRIT accepts applications and awards grants for a wide variety of cancer-related research and for the delivery of cancer prevention programs and services by public and private entities located in Texas.

To date, CPRIT has awarded more than $1.89 billion in grants to Texas researchers, institutions and organizations. CPRIT provides funding through its academic research, prevention and product development research programs. Programs made possible with CPRIT funding have reached all 254 counties of the state, brought 135 distinguished researchers to Texas, advanced scientific and clinical knowledge, and provided more than 4 million life-saving education, training, prevention and early detection services to Texans.

More information about CPRIT is available at www.cprit.texas.gov. Follow CPRIT on Twitter @CPRITTexas and Facebook.
CPRIT OVERSIGHT COMMITTEE

CPRIT is governed by nine dedicated Texans who together comprise the Oversight Committee. Oversight Committee members are appointed by the Governor, the Lieutenant Governor, and the Speaker of the House to serve staggered terms. The Oversight Committee meets at least once every quarter.

Will Montgomery, Dallas, Presiding Officer
Donald “Dee” Margo, El Paso, Assistant Presiding Officer
Amy Mitchell, Austin, Secretary
Angelos Angelou, Austin
David Cummings, MD, San Angelo
Pete Geren, Fort Worth
Ned Holmes, Houston
Mahendra C. Patel, MD, San Antonio
Craig Rosenfeld, MD, Dallas

CPRIT EXECUTIVE TEAM

CPRIT’s efforts are guided by an executive team that is committed to fulfilling CPRIT’s mission to find and fund the best cancer prevention, academic research, and product development research projects in Texas.

Wayne Roberts, Chief Executive Officer
Kristen Doyle, Deputy Executive Officer and General Counsel
Vince Burgess, Chief Compliance Officer
Rebecca Garcia, PhD, Chief Prevention and Communications Officer
James K.V. Willson, MD, Chief Scientific Officer
Michael Lang, Chief Product Development Officer
Heidi McConnell, Chief Operating Officer
## MONDAY, NOVEMBER 13

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 A.M.</td>
<td>Opening Session</td>
<td>Ballroom A</td>
<td><strong>CPRIT: Today and Tomorrow</strong>&lt;br&gt;Wayne Roberts, Chief Executive Officer, CPRIT</td>
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<tr>
<td></td>
<td><strong>Welcome - CPRIT Oversight Committee Presiding Officer</strong>&lt;br&gt;Will Montgomery, CPRIT</td>
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</tr>
<tr>
<td>9:00 A.M.</td>
<td>Opening Session</td>
<td>Ballroom A</td>
<td><strong>Precision Medicine in Cancer Prevention, Screening, and Treatment: The HPV Paradigm</strong>&lt;br&gt;Douglas Lowy, MD, National Cancer Institute (NCI)</td>
</tr>
<tr>
<td>9:05 A.M.</td>
<td>Opening Session</td>
<td>Ballroom A</td>
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<tr>
<td>9:50 A.M.</td>
<td>General Session</td>
<td>Ballroom A</td>
<td><strong>Evolving Developments In Immunotherapy: A Look at the Future</strong>&lt;br&gt;Moderator: Patrick Hwu, MD, UT MD Anderson Cancer Center&lt;br&gt;Harpreeet Singh, PhD, Immatics US, Inc.&lt;br&gt;Helen Heslof, MD, Baylor College of Medicine&lt;br&gt;Jennifer Wargo, MD, MMSc, UT MD Anderson Cancer Center</td>
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<td>10:00 A.M.</td>
<td>Lunch Provided</td>
<td>Ballroom B &amp; Arbor</td>
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<tr>
<td>11:30 A.M.</td>
<td>Lunch Provided</td>
<td>Ballroom B &amp; Arbor</td>
<td><strong>No Program</strong></td>
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<tr>
<td>12:30 P.M.</td>
<td>Concurrent Session</td>
<td>Ballroom A</td>
<td><strong>Epigenome-Environment Interactions — Impact on Cancer Risk and Targets for Prevention</strong>&lt;br&gt;Cheryl Lyn Walker, PhD, Baylor College of Medicine&lt;br&gt;Margaret Kripke, PhD, UT MD Anderson Cancer Center</td>
</tr>
<tr>
<td>12:30 P.M.</td>
<td>Product Development Research</td>
<td>Glass Oaks</td>
<td><strong>Product Development Research Company Showcase</strong>&lt;br&gt;Moderator: Mike Lang, CPRIT</td>
</tr>
<tr>
<td>1:30 P.M.</td>
<td>Concurrent Session</td>
<td>Ballroom A</td>
<td><strong>Liquid Biopsies: State of the Science for Early Detection, Diagnosis</strong>&lt;br&gt;Moderator: Stanley R. Hamilton, MD, UT MD Anderson Cancer Center&lt;br&gt;Anirban Maitra, MBBS, UT MD Anderson Cancer Center&lt;br&gt;Victor Ugaz, PhD, Texas A&amp;M University</td>
</tr>
<tr>
<td>2:45 P.M.</td>
<td>Product Development Research</td>
<td>Glass Oaks</td>
<td><strong>Product Development Research Company Showcase - cont’d</strong></td>
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<tr>
<td>3:00 P.M.</td>
<td>Concurrent Session</td>
<td>Posters</td>
<td><strong>Poster Group A</strong></td>
</tr>
<tr>
<td>4:45 P.M.</td>
<td>Product Development Research</td>
<td>Glass Oaks</td>
<td><strong>Product Development Research Company Showcase - cont’d</strong></td>
</tr>
</tbody>
</table>
### TUESDAY, NOVEMBER 14

| 8:00 A.M. | Opening Session | Ballroom A | *When Precision Medicine Is Not So Precise*  
Neil Spector, MD, Duke Cancer Institute |
|-----------|----------------|------------|---------------------------------------------|
| 8:45 A.M. | General Session | Ballroom A | *Diet, Obesity, Lifestyle and Cancer: Risk and Survival*  
Moderator: Ross Brownson, PhD, Washington University in St. Louis  
Charles S. Fuchs, MD, MPH, Yale Cancer Center, Smilow Cancer Hospital  
Graham A. Colditz, DrPH, MD, MPH, Washington University in St. Louis |
| 10:00 A.M. | Posters | Rio Grande Hall | *Poster Group B* |
| 11:30 A.M. | Lunch Provided | Ballroom B & Arbor | No Program |
| 12:30 P.M. | Concurrent Session | Ballroom A | *Progress on Childhood Cancer Research*  
Moderator: Stephen X. Skapek, MD, UT Southwestern Medical Center  
Abby Berenson, MD, PhD, UT Medical Branch at Galveston  
Barry Maurer, MD, PhD, Texas Tech University Health Sciences Center  
Brendan Lee, MD, PhD, Baylor College of Medicine  
James Amatruda MD, PhD, UT Southwestern Medical Center  
Joshua Mendell, MD, PhD, UT Southwestern Medical Center  
Peter Houghton, PhD, UT Health Science Center at San Antonio |
| | | Prevention Wedgwood | *Dissemination and Implementation Science for Cancer Control: Realizing the Potential of Discoveries*  
Ross Brownson, PhD, Washington University in St. Louis |
| 1:15 P.M. | Product Development Research | Glass Oaks | *Clinical Trial Design*  
George Peoples, COL (ret), MD, FACS, Cancer Insight and the Cancer Vaccine Development Program (CVDP), Metis Foundation |
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Venue</th>
<th>Title</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:20 P.M.</td>
<td>Concurrent Session</td>
<td>Ballroom A</td>
<td><strong>Progress on Childhood Cancer Research - cont’d</strong></td>
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</tr>
<tr>
<td></td>
<td>Prevention</td>
<td>Wedgwood</td>
<td><strong>Approaches to Community Needs Assessment and Stakeholder Engagement</strong></td>
<td>Billy U. Philips, PhD, MPH, Texas Tech University Health Sciences Center, Kenneth Stewart, PhD, Angelo State University</td>
</tr>
<tr>
<td>2:05 P.M.</td>
<td>Product Development Research</td>
<td>Glass Oaks</td>
<td><strong>High Cancer Drug Prices: Causes, Patient Impact and Potential Solutions</strong></td>
<td>Hagop M. Kantarjian, MD, UT MD Anderson Cancer Center</td>
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<tr>
<td>2:25 P.M.</td>
<td>Concurrent Session</td>
<td>Ballroom A</td>
<td><strong>Update on CPRIT-Funded Core Facility Research</strong></td>
<td>James K.V. Willson, MD, CPRIT, Funda Meric-Bernstam, MD, UT MD Anderson Cancer Center, Gaudenz Danuser, PhD, UT Southwestern Medical Center, Martin M. Matzuk, MD, PhD, Baylor College of Medicine, Ben Taub General Hospital, Michael Scheurer, PhD, MPH, Baylor College of Medicine</td>
</tr>
<tr>
<td></td>
<td>Prevention</td>
<td>Wedgwood</td>
<td><strong>Dissemination and Implementation – Strategies and Examples</strong></td>
<td>Rebecca Garcia, PhD, CPRIT, Jane Bolin, PhD, JD, BSH, Texas A&amp;M Health Science Center, Lorraine Reitzel, PhD, FAAHB, University of Houston, Maria Fernandez, PhD, UT Health Science Center at Houston, Rakhshanda Rahman, MD, FRCS, FACS, Texas Tech University Health Sciences Center</td>
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<tr>
<td>3:10 P.M.</td>
<td>Product Development Research</td>
<td>Glass Oaks</td>
<td><strong>Start-up Trials and Tribulations</strong></td>
<td>Matt McManus, MD, PhD, Asuragen, Inc., Fahar Merchant, PhD, Medicenna Therapeutics, Inc., Harpreet Singh, PhD, Immatics US, Inc., Jon Northup, Beta Cat Pharmaceuticals, LLC</td>
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<tr>
<td>3:15 P.M.</td>
<td>Concurrent Session</td>
<td>Ballroom A</td>
<td><strong>CPRIT Academic Research RFA Funding Mechanisms</strong></td>
<td>James K.V. Willson, MD, CPRIT</td>
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</tr>
</tbody>
</table>
MONDAY, NOVEMBER 13

8:30 – 9:00 AM - OPENING SESSION

Where: Ballroom A  CPRIT: Today and Tomorrow

Wayne Roberts
Chief Executive Officer
Cancer Prevention and Research Institute of Texas

Wayne Roberts was named Chief Executive Officer of the Cancer Prevention and Research Institute of Texas (CPRIT) in November 2013 after serving since December 2012 as the Interim Executive Director.

Prior to four years with The University of Texas Health Science Center at Houston as Associate Vice President for Public Policy, Mr. Roberts’ career was weighted towards public finance and budget, especially with respect to higher education. He held numerous senior positions under Governor Rick Perry in which, among other things, he authored the white paper and draft legislation creating the Texas Emerging Technology Fund to catalyze economic development, including transferring research conducted at universities to the Texas marketplace.

Mr. Roberts served Governor George W. Bush as Deputy and Acting State Budget Director. He was Lieutenant Governor Bob Bullock’s special assistant for budget and human services following 18 years with the Legislative Budget Board.

He received a B.A.with honors and special honors in government from The University of Texas at Austin and a masters from the Lyndon B. Johnson School of Public Affairs at UT.

Welcome - CPRIT Oversight Committee Presiding Officer

Will Montgomery
Presiding Officer, Oversight Committee
Cancer Prevention and Research Institute of Texas

Mr. Montgomery is a partner at Jackson Walker LLP, where his practice focuses on commercial litigation and arbitration. He is experienced in all aspects of litigation, including jury and non-jury trials, arbitration, and mediation.

In recent comments, he expressed a personal stake in helping to steer CPRIT toward success in championing treatments and cures for cancer: “Cancer is a scourge that has touched families throughout Texas, including my own,” Montgomery told D Healthcare Daily. “My father was a cancer researcher, ironically contracting cancer late in his life. My brother recently died of cancer. I am honored to have the opportunity to serve the state and to help accomplish CPRIT’s mission to educate, prevent, and discover causes and possible cures for cancer.”

Mr. Montgomery was admitted to the Texas State Bar in 1984. He received his BA and his MA degrees from Stanford University. He received his JD degree from the University of Chicago.
9:05 – 9:50 AM - OPENING SESSION
Where: Ballroom A  Topic: Precision Medicine in Cancer Prevention, Screening, and Treatment: The HPV Paradigm

Precision (personalized) medicine often refers to interventions for the treatment of established disease, such as cancer. However, the principles of precision medicine—interventions based on a molecular understanding of disease—are equally relevant to cancer prevention and screening. Recognition of HPV infection as the main cause of cervical cancer and a high proportion of several other cancers has led to several successful etiology-based interventions. They include: 1) primary prevention of HPV-associated cancers by FDA-approved HPV vaccines; 2) secondary prevention of cervical cancer by FDA-approved HPV-based screening; and 3) treatment of HPV-associated cancer by candidate interventions directed against HPV-encoded proteins in the cancer. The treatment approach may improve the outlook and clinical outcome for patients who develop HPV-associated cancers, while the prevention and screening approaches have the long-term potential to eliminate these cancers as a worldwide public health problem. The relevance of these advances to other cancers, including tumors not attributable to infectious oncogenic agents, will be discussed.

Douglas Lowy, MD
Chief, Laboratory of Cellular Oncology and Senior Investigator Head, Signaling and Oncogenesis Section
National Cancer Institute

Since 2010, Dr. Lowy has helped to lead NCI’s key scientific initiatives. A cancer researcher for more than 40 years, Dr. Lowy received the National Medal of Technology and Innovation from President Obama in 2014 for his research that led to the development of the human papillomavirus (HPV) vaccine. As chief of the Laboratory of Cellular Oncology in the Center for Cancer Research at NCI, Dr. Lowy’s research includes the biology of papillomaviruses and the regulation of normal and neoplastic growth. For his pioneering work, Dr. Lowy has received numerous honors in addition to the National Medal, including the 2017 Lasker-DeBakey Clinical Medical Research Award, the 2011 Albert B. Sabin Gold Medal Award and the Federal Employee of the Year Award in 2007 from the Partnership for Public Service.

10:00 – 11:30 AM - GENERAL SESSION
Where: Ballroom A  Topic: Evolving Developments In Immunotherapy: A Look at the Future

Creative new ways to stimulate the immune system against cancer, including molecularly engineering T-cells continue to emerge daily. The dramatic and long-lasting results seen in responding patients have bolstered the efforts of the scientific community. Attend this session to hear the current state of the art in immunotherapy as well as future directions.

Moderator

Patrick Hwu, MD
Head of the Division of Cancer Medicine; Chair, Departments of Melanoma and Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center

Dr. Hwu is a tumor immunologist focused on the areas of vaccines, adoptive T-cell therapies, and immune resistance. His research and clinical efforts have led to insights and advances in the understanding of the interactions between tumors and the immune system, and the development of cellular therapies. He is the principal investigator on several peer-reviewed grants including NIH translational immunotherapy R01s. Based on the work in his lab, several ongoing clinical trials have resulted, including a trial of T-cells gene-modified to enhance resistance against TGF-b. Most recently, his preclinical studies have focused on combinations of immune checkpoint blockade and T-cell therapy, as well as rational combinations of targeted therapies and immunotherapies. In recognition of his outstanding contributions to cancer research, Dr. Hwu has held endowed positions since joining the institution. He currently holds the Sheikh Mohammed Bin Zayed Al Nahyan Distinguished University Chair at MD Anderson.
Speakers

Harpreet Singh, PhD
Chief Executive Officer
Immatics US, Inc.

With help from a CPRIT grant, Dr. Singh co-founded Immatics US, Inc. As Immatics Biotechnologies GmbH managing director and chief scientific officer, he is dedicated to the translation of science into highly innovative cancer immunotherapeutics. At Immatics GmbH, Dr. Singh leads a team dedicated to target and TCR discovery, immunology, manufacturing, and translational development. Dr. Singh holds numerous patents and is the co-author of 30 publications in peer-reviewed journals, including Nature Medicine, Nature Biotechnology, Journal of Experimental Medicine, and Brain and Blood.

Helen Heslop, MD
Associate Director for Clinical Research
Dan L. Duncan Cancer Center, Baylor College of Medicine

Dr. Heslop oversees several peer-reviewed clinical research projects, including: an NCI-funded program project grant (Enhancing T-Cell Therapy of Cancer), a SPORE grant in Lymphoma, and a Leukemia and Lymphoma Society Specialized Center of Research (SCOR) award. A Doris Duke Distinguished Clinical Scientist, Dr. Heslop has extensive experience in mentoring both clinical and laboratory trainees. She has extensive experience with clinical cell therapy studies, and serves with Dr. Malcolm Brenner and Bambi Grilley as sponsor for more than 20 active cell and gene therapy INDs.

Jennifer Wargo, MD, MMSc
Associate Professor, Department of Surgical Oncology, Division of Surgery and Department of Genomic Medicine, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

Dr. Wargo’s research focuses on critical studies to better understand the effects of BRAF inhibition on immune responses in melanoma, and establishing a unique set of serial tumor biopsies and blood samples from patients enrolled in clinical trials on BRAF inhibitors. Through analysis of these samples, she has contributed significantly to the world literature regarding resistance mechanisms and the effect of targeted therapy on anti-tumor immunity. In September 2013, MD Anderson Cancer Center recruited Dr. Wargo to continue this work and to build a program to collect serial biopsies in patients with melanoma and other cancers on targeted therapy and immunotherapy, and to better understand responses to therapy and to develop novel strategies to combat resistance.

11:30 AM – 12:30 PM - LUNCH PROVIDED - NO PROGRAM

Where: Ballroom B & Arbor
Our expanding knowledge about the role of epigenomic alterations in cancer has opened the door for understanding how epigenome-environment interactions drive the development of this disease, and provided new opportunities for identifying strategies that can exploit epigenomic plasticity for cancer prevention. Importantly, environmental exposures that occur early in life can have a profound effect on the epigenome of developing tissues, altering the epigenome in ways that persist long after the initial exposure. This type of “developmental reprogramming” of the epigenome can persist into adulthood, and dramatically increase cancer risk across the life course. To address this important new area of research, Baylor College of Medicine has established the Center for Precision Environmental Health, where faculty work to understand the causes of cancer and other diseases through research at the intersection of genetics/epigenetics, environmental health and data science (GxExD). Attend this session to hear more about recent insights into how the environment affects cancer risk, and how our growing knowledge in the area of epigenome-environment interactions is presenting new opportunities for interventions targeting the epigenome to reduce cancer risk.

Cheryl Lyn Walker, PhD  
Director, Center for Precision Environmental Health  
Baylor College of Medicine  

A renowned molecular biologist, Dr. Walker joined the faculty of Baylor College of Medicine to develop its Center for Precision Environmental Health. She also currently directs the NIEHS Center for Translational Environmental Health Research, and serves on the board of Scientific Advisors for the National Cancer Institute and is a member of the National Academy of Sciences, Medicine and Engineering Committee on Gulf War and Health. An international leader in environmental carcinogenesis and elucidating molecular mechanisms of disease, Dr. Walker’s studies on the role of the epigenome in gene-environment interactions have yielded significant insights into mechanisms by which early life exposures influence health and disease across the life course. Her work has also led to the discovery of new tumor suppressor functions in the cell and a dual role for the cell’s epigenetic machinery in regulating both chromatin and the cytoskeleton. She has been recognized with the Dallas-Ft. Worth Living Legend Faculty Achievement Award in Basic Research from MD Anderson Cancer Center, the Cozzarrelli Prize from the National Academy of Sciences, the 2015 Outstanding Distinguished Scientist Award from Sigma Xi, and the 2016 Leading Edge in Basic Research Award from the Society of Toxicology.

Margaret Kripke, PhD  
Professor Emerita  
The University of Texas MD Anderson Cancer Center  

Best known for her work in immunology of skin cancer, Dr. Kripke showed that chronic exposure to UV radiation produces cancers that are highly antigenic and that immune alterations induced by UV are responsible for tumor survival and spread. She discovered that mice exposed to UV radiation develop a selective, systemic immune suppression, and her work led to a new field of photoimmunology. Dr. Kripke’s research has provided insight into how an immune system compromised by UV radiation contributes to the development of melanoma and increased vulnerability to infectious diseases.

Dr. Kripke established a new basic research department at The University of Texas MD Anderson Cancer Center and later served as vice president for academic programs and executive vice president and chief academic officer. She has been a leader in many organizations dedicated to research and collaboration and has contributed substantially to the field of environmental science. She served as CPRIT’s Chief Scientific Officer from 2012 to 2015.
12:30 – 1:30 PM - CONCURRENT SESSION 2 - PRODUCT DEVELOPMENT RESEARCH

Where: Glass Oaks  
Topic: Product Development Research Company Showcase

CPRIT has invested in the development of over 30 novel cancer products including immunotherapies, drugs, biologics, molecular diagnostics, devices, and services. This session provides an opportunity for attendees to hear about the research and development of promising new products and services. Company representatives will provide 15-minute overviews of their innovative new offerings. Each company will have a table set up in the Glass Oaks Ballroom to answer questions and interact with attendees.

Mike Lang  
Chief Product Development Research Officer  
Cancer Prevention and Research Institute of Texas

Mike Lang leads CPRIT’s product development research program, designed to accelerate the progression of new cancer drugs, diagnostics, and therapies from the laboratory into clinical practice. His multi-state experience includes founding and serving as chief executive officer of a cancer diagnostic company, serial entrepreneurship, and managing a portfolio for an early stage investment. Prior to joining CPRIT in November 2015, Mr. Lang was the founder and CEO of NanoVision, a cancer diagnostics company. He headed business development at the venture capital-funded wound healing company Gilatech, where he led its novel biomaterial therapy. Lang oversaw a company restructuring as president of Dallas-based Galt Medical, served as a product manager at Johnson & Johnson, and was vice president of business development at BioEnterprise, where he directed the startup and growth of early stage firms. Mr. Lang has a BS in biomedical engineering from Northern Arizona University and a MBA from Arizona State University.

1:45 – 2:45 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH/PREVENTION

Where: Ballroom A  
Topic: Liquid Biopsies: State of the Science for Early Detection, Diagnosis

Liquid biopsies to test for tumor products in blood and other body fluids promise a less invasive way of evaluating patients with cancer than traditional methods. Although numerous companies currently market liquid biopsies, commercial applications remain largely limited to improving treatment selection for late-stage cancers and monitoring for recurrence. Research and funding are increasing as companies work to improve methodologies and results, as well as to broaden the market. Pushing development into earlier cancer stages for screening, surveillance and diagnosis has high priority. Attend this session to hear an update on the process as well as presentations of successful examples.

Moderator

Stanley R. Hamilton, MD  
Professor and Head of Pathology and Laboratory Medicine  
The University of Texas MD Anderson Cancer Center

Dr. Hamilton has been involved in research and clinical applications of the molecular pathology of gastrointestinal neoplasms since 1982. Of his 341 peer-reviewed publications, over 200 address this topic, including two of the earliest evaluations of genomics as prognostic markers in colorectal adenocarcinoma. In addition, Dr. Hamilton has been active in the cooperative oncology group clinical trials setting for 25 years as a member of the Eastern Cooperative Oncology Group, now the ECOG-ACRIN Cancer Research Group in the National Clinical Trials Network (NCTN). He has published correlative studies of molecular biomarkers using specimens from ECOG clinical trials. The clinical laboratories at UTMDACC under his direction provided the pre-analytics and analytics for 2,843 tumors for E5202, the first integral-marker phase III clinical trial in colon cancer in the NCI cooperative group setting, and 5,946 tumors for NCI-MATCH (EAY131). Dr. Hamilton is a member of the ECOG-ACRIN Leadership as Deputy Chair for Laboratory Science.
Speakers

Anirban Maitra, MBBS
Professor of Pathology and Translational Molecular Pathology Scientific Director, Sheikh Ahmed Center for Pancreatic Cancer Research Co-Leader, MD Anderson Pancreatic Cancer Moon Shot™
The University of Texas MD Anderson Cancer Center

Dr. Maitra is Professor of Pathology and Translational Molecular Pathology at UT MD Anderson Cancer Center, and Scientific Director of the Sheikh Ahmed Bin Zayed Center for Pancreatic Cancer Research (since August 1, 2013). Over the past decade, his group has made several seminal observations in the biology and genetics of pancreatic cancer. His laboratory has access to large numbers of well annotated samples of pancreatic adenocarcinomas and precursor lesions, as well as human patient derived xenograft models. He also has extensive expertise with genetically engineered mouse models of pancreatic cancer, and with experimental therapeutics and drug development for this disease.

Victor Ugaz, PhD
Professor, Artie McFerrin Department of Chemical Engineering
Texas A&M University

Victor M. Ugaz, Ph.D. is a Professor and Holder of the Charles D. Holland ’53 Professorship in the Artie McFerrin Department of Chemical Engineering at Texas A&M University. He joined the faculty in January 2003, with research interests focused on microfluidic transport phenomena. His research focuses broadly on harnessing the unique characteristics of transport and flow at the microscale, with specific interests in microfluidic flows (both single-phase and nanoparticle suspensions), microchip gel electrophoresis, PCR thermocycling in novel convective flow devices, and construction of 3D vascular flow networks for biomedical applications. Ugaz earned BS and MS degrees in Aerospace Engineering at The University of Texas at Austin, and a PhD in Chemical Engineering from Northwestern University. He currently serves as Chair of the interdisciplinary Master of Biotechnology (MBIOT) program, Assistant Agency Director for Research Development in the College of Engineering at Texas A&M, and has served as past President of the American Electrophoresis Society (AES).

1:45 – 2:45 PM - CONCURRENT SESSION 2 - PRODUCT DEVELOPMENT RESEARCH

3:00 – 4:45 PM - POSTER SESSION A
Where: Rio Grande Hall

3:00 – 4:45 PM - CONCURRENT SESSION - PRODUCT DEVELOPMENT RESEARCH
8:00 – 8:45 AM - OPENING SESSION
Where: Ballroom A  Topic: When Precision Medicine Is Not So Precise

In the prime of life, an avid runner, Dr. Neil Spector, who trained at the top academic institutions became deathly ill from a mysterious illness. His doctors were baffled and attributed his unusual symptoms to stress, with nothing glaringly abnormal showing up on routine laboratory testing. After four years of fighting to stay alive and convince his doctors there was something medically wrong, a diagnosis was finally made and appropriate treatment administered. Dr. Spector will discuss how he miraculously overcame all the odds, the importance of balancing the science of precision medicine and the “art” of medicine and the lessons that he learned as a physician-scientist who found himself on the other side of a highly complex medical healthcare system.

Neil Spector, MD
Director of the Developmental Therapeutics Program, Duke Cancer Institute
Duke University

Author of “Gone in a Heartbeat: A Physician’s Search for True Healing,” Neil Spector, MD, is a leader in applying translational research to the clinical development of molecularly targeted personalized cancer therapies. He broke through conventional thinking to bring new treatment options to the arsenal of breast cancer drugs, fought to include rare subtypes in clinical trials, and worked to develop collaborations that helped transform laboratory successes into real therapies for patients. His application of translational research to the preclinical and clinical development of lapatinib remains an example of how precision oncology can transform treatment of cancer patients, and facilitate the development of targeted cancer therapies. Dr. Spector is currently the Sandra Coates Chair in Breast Cancer Research at the Duke University School of Medicine, leader of the Duke Cancer Institute Developmental Therapeutics Program, and he was selected by his peers as a Komen Research Scholar.

In addition to his research, Dr. Spector continues to see oncology patients and was recently appointed National Director of Precision Oncology for the VA Healthcare System.

8:45 – 10:00 AM - GENERAL SESSION
Where: Ballroom A  Topic: Diet, Obesity, Lifestyle and Cancer: Risk and Survival

Moderator
Ross Brownson, PhD
Professor and Director, Prevention Research Center
Brown School and School of Medicine, Washington University in St. Louis

Chair of a CPRIT Prevention Review Panel, Dr. Brownson is the Bernard Becker professor at Washington University in St. Louis, with appointments in the Brown School and the Alvin J. Siteman Cancer Center. He is currently involved in numerous community-level studies designed to understand and reduce modifiable risk factors such as physical inactivity, obesity, and tobacco use. In particular, he is interested in the impacts of environmental and policy interventions on cancer risk factors and he conducts research on dissemination of evidence-based interventions with a focus on policy settings and health departments. Dr. Brownson has authored nine books and more than 450 peer-reviewed articles.
Charles Fuchs, MD, MPH
Director, Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital
Yale University

An internationally recognized expert in gastrointestinal cancers and cancer epidemiology, Dr. Fuchs was previously professor of medicine at Harvard Medical School and chief of the gastrointestinal oncology division and the Robert T. and Judith B. Hale Chair in Pancreatic Cancer at Dana-Farber Cancer Institute. Dr. Fuchs conducts research in gastrointestinal cancer epidemiology. In addition to studying the influence of diet and lifestyle, his research team is looking at the influence of such biomarkers as insulin-like growth factors, steroid hormones, and polymorphisms of metabolism enzymes on the risk of these cancers. Dr. Fuchs also conducts research assessing various treatment regimens and new drugs for gastrointestinal cancers.

Graham Colditz, DrPH, MD, MPH
Associate Director Prevention and Control
Alvin J. Siteman Cancer Center, Washington University in St. Louis

As an epidemiologist and public health expert, Dr. Colditz has a longstanding interest in the preventable causes of chronic disease, particularly among women. An internationally recognized leader in cancer prevention, Dr. Colditz is interested in strategies to speed translation of research findings to prevention strategies that work. His past research has focused on the health effects of smoking, weight and weight gain, physical activity, diet, and the adverse effects of medications such as postmenopausal hormone therapy, documenting that current use increases risk of breast cancer.

10:00 – 11:30 AM - POSTER SESSION B
Where: Rio Grande Hall

11:30 AM – 12:30 PM - LUNCH
Where: Ballroom B & Arbor

12:30 – 1:15 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH
Where: Ballroom A Topic: Progress on Childhood Cancer Research

With cancer still serving as the leading cause of death from disease among children and adolescents, researchers are working to make progress in key areas. Join this session to hear about specific research projects to develop more effective treatment for childhood cancer and learn about future research and prevention directions.

Moderator
Stephen X. Skapek, MD
Chief, Division of Pediatric Hematology-Oncology, Department of Pediatrics
The University of Texas Southwestern Medical Center

Dr. Skapek believes that caring for children with cancer requires both clinical and research excellence. He leads one of the larger pediatric cancer programs in the United States, comprising some 25 faculty physicians who all have established and growing expertise in specific areas of childhood cancer and blood disorders. He also leads a research lab that focuses on tumor-suppressor genes in soft-tissue sarcomas. Dr. Skapek holds the UT Southwestern Distinguished Chair in Pediatric Oncology Research. He also serves as Medical Director of the Gill Center for Cancer and Blood Disorders at Children’s Medical Center in Dallas. Dr. Skapek serves on several leadership committees for the international Children’s Oncology Group, the world’s largest clinical research organization focused on childhood cancers. He is also a member of the Association for Research and Vision Ophthalmology, the American Society of Pediatric Oncology, and the American Association of Cancer Research.
Speakers

Abbey Berenson, MD, PhD
Director, Center for Interdisciplinary Research in Women’s Health
The University of Texas Medical Branch at Galveston

Dr. Berenson’s research interests involve improving women’s health from puberty to menopause. She has maintained extramural support for her studies in adolescents and young women since 1994. Currently, she is leading cancer prevention projects aimed at increasing uptake of the human papillomavirus (HPV) vaccine. Her projects include offering the vaccine to young women while they are patients on the postpartum unit, providing one-one counseling on HPV, HPV-related cancers, and the HPV vaccine to mothers of children seen in pediatric clinics, and outreach to young men and women in medically underserved areas of the Golden Triangle. She has published 40 papers in peer-review journals and presented her CPRIT projects at a number of conferences, including those in Lisbon and CapeTown.

Barry Maurer, MD, PhD
Associate Professor
Texas Tech University Health Sciences Center

Dr. Maurer is a board-certified pediatric oncologist and academic developmental cancer researcher conducting basic laboratory investigations and early phase clinical trials. His major interests are the cellular mechanisms, translational development, and clinical testing of the cytotoxic retinoid, fenretinide, as a dihydroceramide-increasing agent, both as a single agent and in combination with other modulators of ceramide pathways in adult and pediatric tumor systems. He currently holds two investigator-initiated, FDA investigational new drug applications related to this research.

Brendan Lee, MD, PhD
Chairman, Molecular and Human Genetics
Baylor College of Medicine

As a pediatrician and geneticist, the overall mission of Dr. Lee’s research program is to translate the study of structural birth defects and inborn errors of metabolism into a basic understanding of development, disease and novel therapeutic approaches. His long standing interest has been the study of human inborn errors of metabolism and structural birth defects of the skeleton. In the study of metabolism, he has applied genetic approaches to the study of biochemical genetic disorders (specifically urea cycle disorders) as models of complex disease (those involving nitric oxide dysregulation). In the study of structural birth defects, his research team has discovered paracrine and endocrine signaling pathways that regulate skeletal development including morphogens (TGFb, Wnt and Notch), post-transcriptional regulation by microRNAs, and extracellular matrix protein modifications (e.g., collagen prolyl-hydroxylation), and their contribution to cancers both intrinsic and metastatic to bone.

James Amatruda, MD, PhD
Associate Professor of Pediatrics, Molecular Biology and Internal Medicine
The University of Texas Southwestern Medical Center

A physician-scientist, Dr. Amatruda divides his time between his research laboratory and Children’s Medical Center, Dallas, where he specializes in the care of children with cancer and blood disorders. Research in his lab focuses on understanding the genetic causes of childhood cancers, including genitourinary cancers and sarcomas, using zebrafish models and human genomic approaches. At UT Southwestern, Dr. Amatruda is the Associate Division Director for Research in the Division of Pediatric Hematology-Oncology, and Assistant Director of the Medical Scientist Training Program. He also serves as Chair of the Germ Cell Tumor Biology and Rare Tumors Biology committees in the Children’s Oncology Group.
Joshua Mendell, MD, PhD
Professor, Department of Molecular Biology and Investigator, Howard Hughes Medical Institute
The University of Texas Southwestern Medical Center

Dr. Mendell has made major contributions to the understanding of the mechanisms that govern gene expression in normal physiology and cancer, and his research group has been at the forefront of dissecting the contributions of microRNAs (miRNAs) and other noncoding RNAs to these processes. Dr. Mendell’s laboratory provided one of the first demonstrations that miRNAs function as components of critical oncogenic and tumor suppressor pathways and that miRNAs represent potent and non-toxic anti-cancer therapeutic agents when delivered systemically. More recently, the Mendell laboratory has demonstrated that other types of noncoding RNAs, including long noncoding RNAs, similarly regulate cancer-relevant processes including genomic stability. Dr. Mendell has been the recipient of several awards including the Allan C. Davis Medal for the Outstanding Young Scientist in the State of Maryland in 2007, the AACR Award for Outstanding Achievement in Cancer Research in 2010, and the O’Donnell Award from the Academy of Medicine, Engineering, and Science of Texas in 2016. Dr. Mendell was appointed as an HHMI Early Career Scientist in 2009 and an HHMI Investigator in 2015. In 2011, Dr. Mendell received a Rising Stars Award from the Cancer Prevention and Research Institute of Texas and relocated his laboratory from Johns Hopkins to UT Southwestern Medical Center in Dallas where he is currently a Professor of Molecular Biology and member of the Simmons Cancer Center and Center for Regenerative Science and Medicine.

Peter Houghton, PhD
Professor of Molecular Medicine, Director of Greehey Children’s Cancer Research Institute
The University of Texas Health Science Center at San Antonio

Dr. Houghton received his PhD from the Institute for Cancer Research, London University, and joined St. Jude Children’s Research Hospital where he became Chair, Department of Molecular Pharmacology, and Co-Leader for the Solid Malignancies Program. In 2009 he became Director, Center for Childhood Cancer and Blood Diseases, at The Research Institute at Nationwide Children’s Hospital, Columbus Ohio, and from 2014 has been Director, Greehey Children’s Cancer Research Institute, University of Texas Health Science Center, San Antonio. His work in developmental therapeutics, has focused largely on pediatric sarcomas. Specifically, understanding the role of insulin-like growth factors in the genesis of pediatric sarcomas, and developing approaches to inhibiting these signaling pathways. This focus led him to identify rapamycin and other rapalogs as potent inhibitors of sarcoma cell proliferation, and to map the pathway downstream of mTORC1 that is important for tumor cell proliferation. Another major focus of his work has been developing xenograft models of childhood cancers. He initiated preclinical development of the camptothecin drugs, topotecan and irinotecan that are now standard components of many pediatric clinical protocols. Dr. Houghton was the Principal Investigator of the National Cancer Institute (NCI) sponsored Pediatric Preclinical Testing Program (PPTP), and a member of the Pediatric Preclinical Testing Consortium where he conducts new agent evaluation against pediatric sarcoma and kidney cancer models. He is the PI on a large multi-institutional P01 grant entitled Studies of Childhood Sarcomas as well as other NIH funded grants. Dr. Houghton has over 35 years of experience in preclinical testing. Dr. Houghton has both NIH and industry support for studies involving drug combinations with ionizing radiation using human tumor xenograft models of pediatric cancer.
12:30 – 1:15 PM - CONCURRENT SESSION 2 - PREVENTION
Where: Wedgwood Topic: **Dissemination and Implementation Science for Cancer Control: Realizing the Potential of Discoveries**

This session will explore recent advancements in dissemination and implementation science that are relevant to cancer prevention and control. Participants will expand their understanding of how this science can improve their work. In particular, the session will explore the potential of dissemination and implementation science, gaps in the evidence base, and opportunities for practice- and policy-based research. The session objectives are to: describe the underpinnings of implementation research; explore some dissemination research topics and gaps (illustrated with policy research); and describe resources for building D&I capacity.

**Ross Brownson, PhD**
Professor and Director, Prevention Research Center
Brown School and School of Medicine, Washington University in St. Louis

Chair of a CPRIT Prevention Review Panel, Dr. Brownson is the Bernard Becker professor at Washington University in St. Louis, with appointments in the Brown School and the Alvin J. Siteman Cancer Center. He is currently involved in numerous community-level studies designed to understand and reduce modifiable risk factors such as physical inactivity, obesity, and tobacco use. In particular, he is interested in the impacts of environmental and policy interventions on cancer risk factors and he conducts research on dissemination of evidence-based interventions with a focus on policy settings and health departments. Dr. Brownson has authored nine books and more than 450 peer-reviewed articles.

12:30 – 1:15 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH
Where: Glass Oaks Topic: **Clinical Trial Design**

The session will cover the general concept of clinical trial design for oncology focused trials. In addition to the basic design concepts that have been in practice for years, the session will focus on newer design elements that allow sponsors to reduce the time and cost of therapeutic products clinical trials. Additionally, the session will focus on specific considerations for testing immuno-oncology products, the latest guidance from the FDA, and novel trends that will shape future trial design.

**George Peoples, COL (ret), MD, FACS**
Founder and CEO
Cancer Insight, LLC and the Cancer Vaccine Development Program (CVDP), Metis Foundation

After retiring from 30 years of active duty as a military surgeon and research scientist, Dr. Peoples created Cancer Insight, LLC. The clinical research and development organization currently conducts multiple phase I and II trials at 50 plus sites across the United States. He also continues his work with CVDP discovering, developing, and clinical testing of cancer vaccines. Additionally, Dr. Peoples is a professor of surgery at Uniformed Services University of the Health Sciences and an adjunct professor of Surgical Oncology at MD Anderson Cancer Center. He is the past Chair of the Cancer Program, San Antonio Military Medical Center (SAMMC) and the past Deputy Director of the United States Military Cancer Institute. Dr. Peoples served as the Chief of Surgical Oncology at Walter Reed Amy Medical Center and at SAMMC. He has written extensively on the immune response to cancer with more than 350 peer-reviewed manuscripts, abstracts, and book chapters.
1:20 – 2:05 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH
Where: Ballroom A
Topic: Progress on Childhood Cancer Research - cont.

1:20 – 2:05 PM - CONCURRENT SESSION 2 - PREVENTION
Where: Wedgwood
Topic: Approaches to Community Needs Assessment and Stakeholder Engagement

This session will focus on community health needs assessment models that are evidenced-based and have been shown to be applicable for use in Texas because they offer practical ways to engage communities in cancer prevention, as well as other public and community health initiatives. Dr. Philips will describe the purpose for and overall approach of useful public health models, with special focus on community stakeholders and how to engage them in collaborative efforts to better prevent and educate about cancer. Dr. Stewart will offer an applied example of how these approaches are being used in a rural area to identify priorities, approaches, and partners that have begun to address local and regional cancer needs. Discussion will follow.

Billy U. Philips, PhD, MPH
Executive Vice President
The F. Marie Hall Institute for Rural and Community Health, Texas Tech University Health Sciences Center

Dr. Philips’ work focuses on improving the health and well-being of the communities of Texas using innovative and scholarly research, advanced use of technology, and comprehensive education and outreach. He is also responsible for the direction, implementation, and overall programming of telemedicine for the entire Health Sciences Center including the federally funded TexLa Telehealth Resource Center grant and demonstration projects such as the Telemedicine Wellness Intervention Triage and Referral (TWITR) Project, the Next Generation 9-1-1 Telemedicine Medical Services Pilot Project, and the Frontiers in Telemedicine Training Lab, the only one of its kind in the nation. An established NIH investigator and author of numerous books, peer-reviewed articles, and other scholarly works in community-based research and chronic diseases, Dr. Philips has a long and distinguished career supporting preventive and public health initiatives.

Kenneth Stewart, PhD
Professor/Director of Community Development Initiatives
Angelo State University

Dr. Stewart established ASU’s Community Development Initiatives (CDI) in 2007 and continues to serve as its director. CDI conducts community-based research to advance community development projects in San Angelo, the Concho Valley, and West Texas. Dr. Stewart serves as program evaluator for Access to Breast and Cervical Care for West Texas (ABCC4WT), a CPRIT funded breast and cervical cancer prevention program serving a 21-county area in West Texas. He headed the community-based assessment team that conducted The Community Health Needs Assessment of the Poor and Extremely Poor in West Texas. Completed in 2015, the study revealed numerous gaps between health and behavioral health service capacities and the prevalence of chronic diseases found in the populations living below the poverty line in 20 counties of West Texas. A member of the editorial advisory board for the Rural Health Quarterly, Dr. Stewart has also published several books, numerous peer-reviewed articles, and other scholarly works on social problems, minority-majority group relations, community development, and public health.
1:20 – 2:05 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH

Where: Glass Oaks  Topic: *High Cancer Drug Prices: Causes, Patient Impact and Potential Solutions*

Over the past 10 years, cancer drug costs have increased in an unprecedented fashion. The rapid escalation in cancer care costs has taken a significant toll on patients and families faced with a cancer diagnosis. During this lecture, Dr. Hagop Kantarjian will detail the historical background of high cancer drug prices, discuss potential causes as well as justifications by the pharmaceutical industry, and elaborate on the harm the rising cost has on patients. The session will examine possible solutions to delivering precision-medicine solutions while maintaining an economically sustainable cancer care system.

**Hagop M. Kantarjian, MD**  Professor and Chairman, Department of Leukemia  The University of Texas MD Anderson Cancer Center

Dr. Kantarjian leads the nation’s largest leukemia practice, known for its extensive participation and leadership in developing new treatments through research and clinical trials. Dr. Kantarjian has developed a number of treatments, including chemotherapy combinations and the single agent clofarabine for acute lymphocytic leukemia (ALL); the hypomethylating agent decitabine, approved by the U.S. Food and Drug Administration (FDA) for myelodysplastic syndromes in 2006; liposomal vincristine, FDA-approved in 2012 for ALL; and ruxolitinib, approved for myelofibrosis in 2011. He has also championed multiple targeted therapies for chronic myeloid leukemia (CML), including imatinib, dasatinib, nilotinib, ponatinib, bosutinib, and omacetaxine, all of which received FDA approvals between 2001 and 2012. He is currently developing monoclonal antibodies in adult ALL. On the MD Anderson faculty since 1983, Kantarjian holds the Kelce Margaret Kana Research Chair and is associate vice president of Global Academic Programs. He was recently appointed as the Baker Institute Scholar in Health Policy.

2:25 – 3:10 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH

Where: Ballroom A  Topic: *Update on CPRIT-Funded Core Facility Research*

The goal of this session is to highlight several CPRIT supported core facilities that are developing forward looking strategies to support cancer research in Texas.

**Moderator**

**James K.V. Willson, MD**  Chief Scientific Officer  Cancer Prevention and Research Institute of Texas

Dr. Willson leads the Cancer Prevention and Research Institute of Texas (CPRIT) academic research program in supporting innovation in cancer research and recruiting world-class cancer researchers to Texas institutions. He is nationally renowned for his work in the genetics of colorectal cancer, having spent more than three decades in the field. Dr. Willson’s research led to the development of cell and animal models for human colon cancer that have been key to identifying genetic factors in disease progression. Dr. Willson joined CPRIT in March 2016 following a distinguished career as director of Simmons Comprehensive Cancer Center and associate dean of oncology programs at The University of Texas Southwestern Medical Center. Under his leadership, Simmons Cancer Center became one of only 45 cancer centers in the U.S. to achieve comprehensive status from the National Cancer Institute (NCI). He helped bring the same prestigious designation to Case Comprehensive Cancer Center in Cleveland, where he served as its director from 1994-2004. A graduate of the University of North Carolina at Chapel Hill, Dr. Willson earned his MD from the University of Alabama in 1976. He completed his residency in internal medicine at Johns Hopkins Hospital in 1981 and received additional training at the NCI.
Speakers

Funda Meric-Bernstam, MD
Chair of the Department of Investigational Cancer Therapeutics -- the Phase I Program, and Professor in the Divisions of Cancer Medicine and Surgery, and The Nellie B. Connally Chair in Breast Cancer
The University of Texas MD Anderson Cancer Center

The Medical Director of the Institute for Personalized Cancer Therapy (IPCT), Dr. Meric-Bernstam has a basic and translational research program that is focused on molecular therapeutics, predominantly on PI3K/Akt/mTOR signaling, to delineate the mechanism of action of each agent targeting this pathway and the molecular alterations useful to prospectively identify patients who will benefit most from each agent, and optimal combination therapies. Her research is focused on identifying molecular markers to predict and monitor drug response and novel biomarker-driven combinations. As the Medical Director of the Institute for Personalized Cancer Therapy at MD Anderson, she has not only led large efforts of genomic testing within the institution, but has a) helped build a framework for rapid assessment of actionability of genomic alterations; b) established a Precision Oncology Decision Support Team who can provide point of care input for actionability; c) launched the public website “www.personalizedcancertheraphy.org” providing access to expert curation of information on therapeutic relevance of specific genes/variants; d) created databases and clinical trial alert systems to facilitate accrual to genotype-selected trials across the institution; and e) monitors trial enrollment after genomic testing to identify approaches to obstacles to trial enrollment. She has participated in, as well as led, trials including investigator-initiated trials, cooperative group trials, and industry sponsored trials. These trials have ranged from a window of opportunity trials, neoadjuvant therapy trials, a Phase I and II trials in the advanced cancer setting as well as new surgical techniques, new imaging devices and molecular diagnostics.

Gaudenz Danuser, PhD
Chair of the Lyda Hill Department of Bioinformatics
The University of Texas Southwestern Medical Center

In July 2015 Dr. Danuser was appointed as the inaugural chair of the Lyda Hill Department of Bioinformatics. He also holds the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science. Before moving to UT Southwestern, Dr. Danuser directed research laboratories at ETH Zurich (2002 – 2003), at The Scripps Research Institute in La Jolla (2003 – 2009), and at Harvard Medical School (2009 – 2014). Trained as an engineer (geodetic and electrical engineering/computer science), he entered the field of cell biology as a postdoctoral fellow in the Program for Architectural Dynamics of Living Cells at the MBL in Woods Hole. Since then, he has focused his research on the question of how chemical and mechanical signals integrate in the regulation of cytoskeleton dynamics and membrane trafficking. He has redirected his efforts towards understanding the implications of mechanical and chemical cell shape regulation in migration and survival of the metastatic cell, including the roles mechanical cues play in conferring what his lab calls 'mechanical drug resistance’. His contributions to cell biology and biophysics have been recognized by several awards and honors.

Martin M. Matzuk, MD, PhD
Stuart A. Wallace Chair, Robert L. Moody, Sr. Chair, and Professor
Baylor College of Medicine and Director of Clinical Chemistry, Ben Taub General Hospital

Dr. Matzuk, Director of the Center for Drug Discovery at Baylor College of Medicine and Director of Clinical Chemistry at Ben Taub General Hospital, is recognized for his elucidation of TGFβ superfamily, germ cell, and hormonal signaling pathways in cancer and reproductive medicine using functional genomics approaches. He has published more than 320 papers (including over 25 papers in Cell, Nature, and Science journals), generated over 100 mouse models, lectured in excess of 170 symposia in 27 countries, and has been supported continuously by the NIH since 1991. Based on Google Scholar, 100 of his papers have been cited over 100 times, and 25 papers have been cited over 400 times. Dr. Matzuk’s other honors include the Richard Weitzman Award from the Endocrine Society, HypoCCS Award from Eli Lilly, Society for the Study of Reproduction Research Award, Pfizer Outstanding Investigator Award from the American Society for Investigative Pathology, Roy Greep Award from The Endocrine Society, International Fundacion IVI Award in Reproductive Medicine, and a MERIT award from the NIH. He in an inventor on a dozen patents and has a highly successful therapeutic on the market. Dr. Matzuk was elected to the
Michael Scheurer, PhD, MPH
Director, Childhood Cancer Epidemiology and Prevention Program
Associate Professor, Department of Pediatrics, Section of Hematology/Oncology
Baylor College of Medicine

Dr. Scheurer’s research focuses on viruses and immune function as risk factors for cancer development and progression. His laboratory looks for novel ways to identify and catalog molecular markers of viral infection, including host-virus interactions, as risk factors for the development of cancer. He is actively involved with two large international research groups focused on two rare tumors: the Brain Tumor Epidemiology Consortium and the Childhood Leukemia International Consortium. Dr. Scheurer is currently working with other researchers and clinicians at Texas Children’s Cancer Center to develop a statewide study to examine risk factors for childhood brain tumors. He also currently has a research project examining Human papillomavirus (HPV)-associated cancers, in particular cervical cancer, including the examination of the HPV vaccine and its effects on cancer incidence. He has an increasing program looking at Human cytomegalovirus (HCMV) and host immune function in relation to pediatric and adult brain tumors, and he also has an interest in the factors that contribute to the poor prognosis and outcome for brain tumor patients, including neurocognitive decline and other therapy-related toxicities.

2:25 – 3:10 PM - CONCURRENT SESSION 2 - PREVENTION
Where: Wedgwood Topic: Dissemination and Implementation – Strategies and Examples

One of CPRIT’s objectives is to facilitate the dissemination and implementation of successful CPRIT funded projects by supporting the development of resources based on these projects. Four recipients of the Dissemination of CPRIT – Funded Cancer Control Interventions (DI) award will discuss strategies and processes for the effective adaptation and implementation of their projects as well as showcase resources and products to assist those interested in adapting and implementing their evidence-based interventions while maintaining fidelity to the original program.

Moderator
Rebecca Garcia, PhD
Chief Prevention and Communications Officer
Cancer Prevention and Research Institute of Texas

Dr. Rebecca Garcia leads CPRIT’s prevention and communications efforts. Ten percent of CPRIT’s total funding is dedicated to evidence-based prevention services. Her responsibilities include directing the prevention program and fostering collaboration among the cancer and disease prevention community to maximize CPRIT’s impact. In addition, she is responsible for overseeing CPRIT’s strategic communications efforts. Prior to joining CPRIT in August of 2009, she served as Vice President, Continuing Professional Development, for Physicians’ Education Resource (PER), a medical education and communications company. Previously, Dr. Garcia was Vice President of Health Sciences for the Susan G. Komen for the Cure where she managed Komen’s scientific research grants and education programs. Dr. Garcia attended the University of Texas at Austin and received a bachelor’s degree in medical technology from the University of Texas Health Science Center at Dallas. She obtained a master’s degree in Biomedical Communications at the University of Texas Health Science Center at Dallas and a doctorate from the Department of Higher Education at the University of North Texas.
Speakers

Jane Bolin, PhD, JD, BSH
Center Director, Health Policy and Management
Texas A&M Health Science Center

Dr. Bolin has served as co-principal investigator on three CPRIT cancer prevention grants on screening for colorectal, breast and cervical cancer in a low-income uninsured population and PI on one dissemination grant from the Cancer Prevention and Research Institute of Texas. She is also the director of the federally funded Southwest Rural Health Research Center at the Texas A&M School of Public Health, conducting policy-relevant research for the benefit of rural and underserved areas of Texas and the nation. As a professor at the Texas A&M School of Public Health, Dr. Bolin’s other academic interests include public health law, health disparities, evidence-based interventions, community-based participatory research and chronic disease, particularly diabetes.

Lorraine Reitzel, PhD, FAAHB
Principal Investigator, Department of Psychological, Health & Learning Sciences
University of Houston

Dr. Reitzel’s research program focuses on better understanding the social determinants of health and health risk behaviors, as well as the specific biopsychosocial mechanisms that account for disparities in health risk behaviors and health outcomes. Her CPRIT-supported work is focused on the dissemination and implementation of a multi-component tobacco-free workplace program within behavioral health centers across Texas. She co-founded and currently co-directs the HEALTH Research Institute, a hub for the university’s community-informed translational research aimed at reducing health disparities and promoting health equity in Houston. She has published more than 110 peer-reviewed empirical articles, is a fellow of the American Academy of Health Behavior, and serves as a Chair of an Institutional Review Board at her academic institution.

Maria Fernandez, PhD
Director, Center for Health Promotion and Prevention Research
The University of Texas Health Science Center at Houston

An internationally known expert in the field of health promotion and cancer control and prevention, Dr. Fernandez has extensive experience in community-based participatory research in cancer control and prevention among underserved populations. She has conducted studies ranging from the description of conceptual models to the development and evaluation of interventions to increase cancer control and prevention. She has also worked to understand and accelerate the use of evidence-based interventions in real-world settings. Dr. Fernandez has received more than $12 million in funding as a principal investigator during the past five years and collaborates as a co-investigator on other studies. Her work is featured in 106 peer-reviewed publications and several book chapters. She also co-authored the book Planning Health Promotion Programs: An Intervention Mapping Approach.

Rahkshanda Rahman, MD, FRCS, FACS
Director of the Amarillo Breast Center of Excellence and Professor of Surgery, School of Medicine
Texas Tech University Health Sciences Center

Dr. Rahman leads a CPRIT-funded prevention project, Access to Breast and Cervical Care for West Texas, which provides screenings and education for residents in 26 Texas Panhandle counties. She joined the Texas Tech University Health Sciences Center (TTUHSC) in 2009 after serving as the founder and director of the interdisciplinary breast fellowship program at the University of Massachusetts. At TTUHSC, Dr. Rahman spearheaded formation of the first nationally accredited Breast Center of Excellence in the Texas Panhandle. Currently, she is the director of the Amarillo Breast Center of Excellence and professor of surgery for the TTUHSC School of Medicine. Dr. Rahman serves on numerous local and national boards and committees including the American Society of Breast Surgeons and the Amarillo Area Breast Health Coalition. She graduated from the Aga Khan University Medical College in Karachi, Pakistan, where she completed her internship and residency. She then spent several years furthering her studies, completing fellowships in breast and general surgery in 2001 at Aga Khan, followed by another fellowship at the University of Arkansas for the medical sciences division of surgical oncology.
Companies engaged in early-stage development often face an uphill battle. Sometimes it is years before a drug, product or service reaches the market, so pre-revenue companies must survive by periodically tapping investors for cash. Then they must navigate the turbulence of clinical trial results that can either make or break them. Clinical trials and the rules that govern them are coming under pressure for an overhaul. With the odds sometimes against them, how do start-up companies manage and secure funding and reach success? Attend this lively panel discussion on start-up trials and tribulations.

Moderator

Matt McManus, MD, PhD
Chief Executive Officer
Asuragen, Inc.

Dr. McManus joined Asuragen in August 2014 with more than 20 years of clinical diagnostic leadership experience, and was previously the CEO and president of PrimeraDx, Inc., a molecular diagnostics company marketing a novel, multiplexed, multi-modal, molecular diagnostics instrument for oncology, infectious disease, and genetic testing. Dr. McManus also served as head of Cleveland Clinic Laboratories and chief operating officer of the Pathology and Laboratory Medicine Institute at the Cleveland Clinic. He received an MD and PhD from the University of Pennsylvania School of Medicine, MBA from Boston College and his bachelor’s from the College of the Holy Cross.

Speakers

Fahar Merchant, PhD
Chairman, President, CEO
Medicenna Therapeutics, Inc.

Dr. Merchant is a 25-year biotech veteran, a serial entrepreneur and co-founder of Medicenna. Previously, he was president and CEO of Protox Therapeutics where he established a late clinical stage urology company. At Protox, he raised more than $70 million through multiple PIPEs, including a $35 million investment by Warburg Pincus. In 1992, he co-founded IntelliGene Expressions, Inc., a biologics CDMO, and built it to one of the fastest growing companies in Canada. In 2000, by strategic in-licensing, he co-founded Avicenna Medica, Inc., a clinical stage oncology company that was sold a year later to KS Biomedix (LSE) for $90 million. Dr. Merchant was CTO and Director of KS Biomedix until its acquisition by Xenova. Dr. Merchant has closed several transactions valued at more than $300 million.

Harpreet Singh, PhD
Chief Executive Officer
Immatics US, Inc.

With help from a CPRIT grant, Dr. Singh co-founded Immatics US, Inc. As Immatics Biotechnologies GmbH managing director and chief scientific officer, he is dedicated to the translation of science into highly innovative cancer immunotherapeutics. At Immatics GmbH, Dr. Singh leads a team dedicated to target and TCR discovery, immunology, manufacturing, and translational development. Dr. Singh holds numerous patents and is the co-author of 30 publications in peer-reviewed journals, including Nature Medicine, Nature Biotechnology, Journal of Experimental Medicine, and Brain and Blood.
Jon Northup  
Chief Executive Officer  
Beta Cat Pharmaceuticals, LLC

Currently, Mr. Northup serves as CEO of several translational oncology companies working on novel cancer therapies from bench to bed, as well as CEO of Indigo Clinical Research, a clinical data services company in India. Mr. Northup is a published author with several articles and frequent presentations within the industry as well as two books – “The Pharmaceutical Industry” chapter in The Business of Healthcare Innovation and Prescription Pricing in Chain and Independent Pharmacies. Mr. Northup worked for Eli Lilly and Company in a variety of executive positions in Corporate Strategy, Business Development, Marketing, and Sales for more than 28 years. During that time, he led 50 collaborations with other pharmaceutical and biotech companies, and participated on the launch team of many Lilly products, including Prozac, Axid, Humatrope, and Humulin.

3:15 – 4:00 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH

Where: Ballroom A  
Topic: CPRIT Academic Research RFA Funding Mechanisms

 Attend this session to hear about current and future funding opportunities for academic research.

James K.V. Willson, MD  
Chief Scientific Officer  
Cancer Prevention and Research Institute of Texas

Dr. Willson leads the Cancer Prevention and Research Institute of Texas (CPRIT) academic research program in supporting innovation in cancer research and recruiting world-class cancer researchers to Texas institutions. He is nationally renowned for his work in the genetics of colorectal cancer, having spent more than three decades in the field. Dr. Willson’s research led to the development of cell and animal models for human colon cancer that have been key to identifying genetic factors in disease progression. Dr. Willson joined CPRIT in March 2016 following a distinguished career as director of Simmons Comprehensive Cancer Center and associate dean of oncology programs at The University of Texas Southwestern Medical Center. Under his leadership, Simmons Cancer Center became one of only 45 cancer centers in the U.S. to achieve comprehensive status from the National Cancer Institute (NCI). He helped bring the same prestigious designation to Case Comprehensive Cancer Center in Cleveland, where he served as its director from 1994-2004. A graduate of the University of North Carolina at Chapel Hill, Dr. Willson earned his MD from the University of Alabama in 1976. He completed his residency in internal medicine at Johns Hopkins Hospital in 1981 and received additional training at the NCI.

3:15 – 4:00 PM - CONCURRENT SESSION 2 - PREVENTION

Where: Wedgwood  
Topic: Dissemination and Implementation – Strategies and Examples (cont’d)

3:15 – 4:00 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH

Where: Glass Oaks  
Topic: Start-up Trials and Tribulations - cont’d
Renaissance Austin Hotel

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ABSTRACTS

Academic Research
Cancer Biology (Abstracts 1–120) .............................................. 29
CPRIT Core Facility (Abstracts 121 through 156) ......................... 60
Etiology/Early Detection/Diagnosis (Abstracts 157 through 197) ....... 70
Prevention/Cancer Control and Survivorship (Abstracts 198 through 229) .... 81
Treatment/Therapeutics (Abstracts 230 through 296, 420 and 421) .... 90

Product Development Research
Detection and Diagnostics (Abstracts 297–307) .......................... 109
Treatments and Therapeutics (Abstracts 308–335) ......................... 112

Prevention
Primary Prevention (Abstracts 336 through 363) ............................ 119
Early Detection and Screening (Abstracts 364 through 410) .............. 127
Survivorship (Abstracts 411 through 419) .................................. 140
1. **CPRIT Grantee Poster Session A**

**Role of yes-associated protein 1 (YAP1) in human pancreatic ductal adenocarcinoma initiation and progression**

*Xue Yin, The University of Texas Health Science Center at San Antonio; J. Liu; N. Akamatu; M. Nipper; P. Wang*

**Introduction:** Understanding the molecular mechanisms underlying pancreatic ductal adenocarcinoma (PDAC) initiation and progression is an urgent need to achieve more effective diagnosis and treatment to this deadly disease. We have developed a computational pipeline to identify expressed polypeptides in cancers, which YAP1 promotes PDAC development and progression. Lentiviruses carrying inducible shYAP1 will be transduced into AD cells to study whether YAP1 is required for AD cell proliferation, and Kras-induced prolonged proliferation. ChIP-PCR and genome-wide ChIP-seq will be used to identify the mechanism through which YAP1 promotes PDAC development and progression. **Results:** So far, we have found that TGF-beta induces YAP1 expression in primary normal human pancreatic cells. However, treating with TGF-beta inhibitor blocks YAP1 induction and ADM, suggesting that YAP1 is downstream of TGF-beta signaling. **Conclusions:** Successful completion of the project will give us a better understanding of how YAP1 functions in human PDAC initiation and progression. It will provide us opportunities to develop new methods for early detection and treatment of PDAC. *Xue Yin is supported by a pre-doctoral fellowship through CPRIT Research Training Award RP103454.* *Pei Wang is CPRIT scholar and funded by First time faculty award.

2. **CPRIT Grantee Poster Session B**

**Identification and Characterization of a Novel LncRNA-Derived Chromatin Binding Polypeptide in Breast Cancer**

*Shikhanth Gadad, The University of Texas Southwestern Medical Center; V. Malladi; C. Camacho; Y. Peng; W. Kraus*

**Introduction:** Long noncoding RNAs (lncRNAs) play important roles in many cellular processes, such as the regulation of gene expression, cell cycle progression, and cellular identity during embryonic development. LncRNAs have been proposed to act through a variety of molecular mechanisms, although the specific mechanisms are not always clear. Recent studies have indicated that some lncRNAs may engage ribosomes and produce short functional polypeptides. In order to explore the molecular mechanisms of novel lncRNA-derived polypeptides in cancers, we have developed a computational pipeline to scan lncRNAs for short open reading frames (ORFs). We then applied this pipeline to a set of 1,888 lncRNAs expressed in MCF-7 cells, which we identified previously as well as all previously annotated lncRNAs based on LncRNAdb, Ensembl, Gencode, and the Human Body Map. Furthermore, we used mass spectrometry (MS) to identify small expressed polypeptides isolated from MCF-7 cell extracts. We then overlaid the polypeptide information with the short open reading frames from lncRNAs to identify ORFs that are actually translated into polypeptides. In this way, we have identified expressed polypeptides that match ORFs in expressed lncRNAs in MCF-cells. **Results:** We have focused our analyses on one polypeptide, Tumor-Specific Polypeptide 1 (TSP1), which is expressed from a newly annotated lncRNA. The lncRNA encoding TSP1 is transcribed exclusively in normal tissues/cancers. Analysis of the evolutionary conservation across the genomes of sequenced species shows that this lncRNA is conserved only in humans. **Conclusions:** On the basis of sequence conservation, we hypothesize that TSP1 encodes a putative chromatin binding protein. If this is the case, TSP1 could be a novel cancer biomarker, as well as a potential therapeutic target.

3. **CPRIT Grantee Poster Session A**

**Numb prevents a complete EMT by modulating Notch signaling**

*Federico Bocci, Rice University; M. Jolly; S. Tripathi; M. Aguilar; S. Hanash; H. Levine; J. Onuchic*

**Introduction:** Epithelial-Mesenchymal Transition (EMT) plays key roles during organogenesis and development as well as in the progression of many diseases. Cells in a partial EMT or hybrid epithelial/mesenchymal (E/M) phenotype tend to exhibit collective cell migration, forming the clusters of Circulating Tumour Cells - the primary drivers of metastasis. Activation of cell-cell signalling pathways such as Notch fosters a partial or complete EMT, yet the underlying mechanisms remain incompletely understood. **Methods:** Using an integrated computational-experimental approach, we examine the role of Numb – an inhibitor of Notch intercellular signalling – in mediating EMT and the clusters formation of hybrid E/M cells. We developed mechanism-based mathematical models for investigating the role of Numb in mediating EMT both at an individual cell and at a tissue-level. We also knocked down Numb in H1975 cells that can maintain a stable hybrid E/M phenotype in vitro, and examine the clinical significance of Numb in predicting poor survival across cancer types. **Results:** We observed that knockdown of Numb in H1975 cells that display a stable hybrid E/M state is sufficient to induce a full E/M state and push them to a full E/M phenotype. Next, our mathematical model recapitulates this ability of Numb in maintaining a hybrid E/M state, and predicts that Numb can alter the relative frequency of hybrid E/M and mesenchymal cell phenotypes in patients’ tissues. **Conclusions:** Our results indicate that Numb can behave as a phenotypic stability factor (PSF) for a hybrid E/M phenotype by stabilizing hybrid E/M phenotype. Correlation observed between Numb and poor patient survival reinforces the emerging notion that a hybrid E/M, but not necessarily a completely mesenchymal, phenotype associates with elevated tumor progression.

4. **CPRIT Grantee Poster Session B**

**RNA-driven gene fusion in human cancer**

*Sachin Kumar Gupta, Baylor College of Medicine; L. Luo; L. Yen*

**Introduction:** One of the hallmarks of cancer is the formation of oncogenic fusion genes as a result of chromosomal translocations. Fusion genes are presumed to occur prior to fusion RNA expression. However, studies have reported the presence of fusion RNAs (such as the BCR-ABL RNA in leukemia) in individuals who were negative for chromosomal translocations. The observation, that fusion RNA could be present prior to fusion gene, raises the possibility that cellular fusion RNA created by trans-splicing could act as a guide RNA to mediate genomic rearrangement by annealing to regions of both chromosomes. **Methods:** We transiently expressed short chimeric RNAs resembling a portion of TMPRSS2 and ERG gene sequence in LNCaP cells and treated them with various concentrations of DHT for 3 days. **Results:** We designed a mathematical model to quantitatively predict the expression of a chimeric RNA derived from the newly induced TMPRSS2-ERG fusion gene, but not from the short chimeric RNAs exogenously expressed from the plasmids. Long-range genomic PCRs and fluorescence in situ hybridization (FISH) were performed to confirm induced fusion gene and to map the genomic breakpoints. **Conclusions:** Our data provide evidence that expression of a chimeric RNA drives formation of a specified gene fusion via genomic rearrangement in malignant cells. The process is (1) specified by the sequence of chimeric RNA involved, (2) facilitated by physiological hormone levels, (3) permissible regardless of intra-chromosomal or inter-chromosomal fusion, and (4) can occur in normal cells prior to malignant transformation. Furthermore, we identified an endogenous RNA that acts as the ‘initiator’ RNA to induce TMPRSS2-ERG fusion. The characterization of the RNA-driven gene fusion will be presented in further details. **Conclusions:** Our data support a model where the initiator RNA drives formation of chimeric DNA to stabilize a transient RNA/DNA duplex using RNA sequences located in two distant genes. Resolution of such an RNA/DNA duplex by DNA break/repair mechanisms might yield the final gene fusion through recombination in regions prone to DNA breaks. The proposed RNA-driven model may provide a mechanism that can ‘specify’ gene fusion partners in early development, and could have fundamental implications in the biology of mammalian genome stability, as well as in understanding cancer and disease evolution.
A phosphotyrosine switch controls antitumor activity of estrogen receptor b

**Introduction:** ERa and ERb, which are encoded by different genes (ESR1 and ESR2), mediate the diverse physiological effects of estrogens. Despite sequence homology and similar transcriptional activity, these two ER subtypes exert distinct and even opposite biological functions in cancer. ERb1 is well recognized as the estrogen receptor associated with breast tumor growth, whereas ERb1 has an antitumor activity in multiple cancer types including breast, prostate, colorectal, ovarian cancers, and melanoma. Furthermore, current literature indicates both tumor-intrinsice and -extrinsic antitumor activity of ERb. The ERb antitumor activity offers a potential target for anticancer therapies. However, it is not clear how ERb antitumor activity can be rationalized. In recently published work, we identified a phosphotyrosine residue in human ERb, which is highly conserved in all mammalian ERb orthologs, but not present in ERa (alanine in ERa). Importantly, this phosphotyrosine switch controls ERb tumor-intrinsice activity. **Methods:** We generated a whole-body knock-in (KI) mouse model in which the phosphotyrosine residue of endogenous mouse ERb is mutated to phenyalanine. And we utilized the murine melanoma cell line B16F10, colon cancer cell line MC38 and mammary gland tumor cell line M-Wnt1, implanted subcutaneously into syngeneic WT and KI mice for these experiments. **Results:** We found that multiple tumor types grew more robustly in KI recipient mice than in their WT counterparts. Furthermore, melanoma-bearing KI mice displayed more lung micro-metastases than WT control. These data demonstrate that the phosphotyrosine switch is important for ERb tumor-extrinsice antitumor activity. In mouse bone marrow chimeras, we found that tumor growth was significantly faster in KI>WT chimeras (with KI immune cells) versus WT>WT control, suggesting that KI-derived immune cells poorly deterred tumor growth. Preliminary data suggest less cell activation in KI versus WT. **Conclusions:** Taken together, our results identify a previously unrecognized molecular switch that harnesses ERb antitumor activity in both tumor-intrinsice and -extrinsice manners. The implication of our laboratory findings in boosting efficacy of the current immunotherapy will be discussed.

**CPRIT Grantee Poster Session A**

**A functional characterization of genomic glycosylation aberrations in tumor initiation and progression**

**Introduction:** Glycosylation, one of the most common post-translational modifications of proteins, plays a central role in regulating protein function. Emerging evidence suggests altered glycosylation contributes to tumor progression as well as affecting therapy response. Understanding the rules regulating altered glycosylation in cancer may thus provide new insight for the development and implementation of therapy approaches. N-glycosylation occurs at the motif consists of a consensus sequence Asn-X-Thr/Ser, where X is not proline. Missense mutations could potentially lead to a loss of gain of N-glycosylation sites due to disruption or creation of consensus sequences. However, whether N-glycosylation site altering aberrations have functional consequences during tumorigenesis has not been systematically evaluated. The aim of this work is to identify patient samples with the potential to alter N-glycosylation sites in cancer genes and to study their functional consequences. **Methods:** To identify aberrations in N-glycosylation sites, all missense mutations that disrupt or create N-glycosylation consensus sequences in all proteins were computationally identified based on sequence data from The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC). The suite of potential N-glycosylation site aberrations that locate in the extracellular domain of secreted or membrane bound proteins, where N-glycosylation mostly occurs, were put forward for functional characterization based on oncogenic transformation in Ba/F3 and MCF10A cells in the absence of growth factors or cytokines and the effects on motility and invasion in MCF10A. The effects of functional aberrations on the proteome will be assessed using reverse phase protein arrays and drug sensitivity testing experimentally. **Results:** By using an in silico bioinformatic approach, we identified 41011 missense mutations with the potential to disrupt or create N-glycosylation consensus sequences from TCAG and ICGC data sets. Among all potential N-glycosylation site altering mutations, 24882 potential gain and 16156 potential loss of N-glycosylation site mutations located in the extracellular domain of membrane bound proteins. 3144 of the potential loss of N-glycosylation site mutations are experimentally identified or predicted as N-glycosylation sites by the NetNGlyc or the PROSITE pattern predictor based on annotation in UniProtKB/Swissprot. Over 40 potential N-glycosylation site altering mutations in receptor tyrosine kinase and cadherin families were selected and are in the process of testing through the functional pipeline and in migration and invasion assays. **Conclusions:** This study may reveal unexpected roles and mechanisms by which N-glycosylation site altering aberrations contribute to tumor progression and therapy response.

**CPRIT Grantee Poster Session B**

**The effect of focal adhesion on the mechanobiology of lung cancer cell during metastasis**

**Introduction:** A mouse model of human lung adenocarcinoma driven by mutations in K-ras and p53 genes was adapted to investigate the role of mechanics and cellular epithelial-to-mesenchymal transition (EMT) potential. We are particularly interested in the focal adhesion pathway, as the mechanical stimuli from ECM could govern the cell adhesion and migration pivotal steps in EMT and metastasis. Cell-matrix organization resulting from interfering with the formation of focal adhesions was investigated at macro- and ultrastructural levels quantitatively. **Methods:** 344SQ metastatic lung tumor cells, and an integrin beta-1 (ITGB1) knockdown variant were encapsulated in collagen gels under incubated static tensions. Colagen gels with 344SQ cells were treated with dasatinib, a Src inhibitor were investigated. The elastic properties of the gels were measured using mechanical tester. Gel pieces were stained with DAPI and phalloidin for confocal imaging, and cell spatial distribution was determined using image analysis. SEM imaging of the gels was used to determine the cell morphology and collagen alignment. **Results:** Interfering with focal adhesions, either by ITGB1 knock down or inhibiting Src resulted in reduced elastic moduli compared to controls. At the ultrastructural level, blocking the focal adhesion pathway reduced the collagen fiber alignment and induced cellular phenotypic changes, with more cell clustering resembling the non-metastatic epithelial morphology. Additionally, f-actin was over produced and cellular spatial distribution changed to a more clustered pattern. **Conclusions:** Inhibiting the formation of focal adhesions also prevents cells from aligning collagen fibers in the direction of tension to the extent observed in controls, indicating less modulation of ECM. It appears to drive more cell-cell adhesion in 3D culture, resulting in clusters of cells that suggest a reversion to a more epithelial phenotype. The cells cluster within a few days, leaving less time for organizing the neotissue, which as a result is less strong.

**CPRIT Grantee Poster Session B**

**Elevated D-2-hydroxyglutarate during colitis drives progression to colorectal cancer**

**Introduction:** Although the association between inflammatory bowel disease and colorectal cancer is well-established, the pathogenesis of colitis-associated cancer (CAC) is poorly understood. D-2-hydroxyglutarate (D2HG) is produced in the tricarboxylic acid cycle and quickly converted to alpha-ketoglutarate by D-2-hydroxyglutarate dehydrogenase (D2HGDH) and the accumulation of D2HG has been linked to oncogenesis in glioma and acute myeloid leukemia. **Methods:** We utilized quantitative metabolic profiling to detect molecular pathways involved in disease progression from colitis to cancer. To induce CAC, wild-type C57BL/6 male mice were intraperitoneally injected with 7.6 mg/kg azoxymethane (AOM) followed by 2 cycles of 3% dextran sodium sulfate (DSS; 1 week DSS and 3 weeks recovery). Urine was serially collected at baseline, during DSS (colitis stage), and the day before sacrifice (polype stage) and metabolites were analyzed using gas chromatography-mass spectrometry. Expression of D2HGDH was measured in AOM-DSS-treated and control colonic mucosal biopsies from UC patients who progressed to CAC or UC patients remaining dysplasia-free. A subset of mice treated with AOM-DSS was i.p. injected with 25 mg/kg D2HG or vehicle once daily during DSS administration. Severity of colitis (body weight, clinical signs of diarrhea, and presence of blood in the stool) were monitored during DSS and recovery phases. Excised colons were collected for polyp number measurement and embedded for dysplasia scoring. **Results:** In the AOM-DSS model of CAC, urine level of D2HG during colitis correlated positively with subsequent polyp counts and severity of dysplasia. Administration of D2HGDH was decreased during DSS colitis and in UC patients at baseline who progressed to cancer. Mice injected with D2HG exhibited delayed recovery from colitis and severe tumorigenesis. **Conclusions:** D2HG enhances the progression of colitis to colon cancer. Urine D2HG and its metabolite D2HGDH expression as potential novel therapeutic targets to identify patients at risk of progressing from colitis to cancer. The D2HGDH/D2HG pathway provides potential novel therapeutic targets for the treatment of CAC.
Unraveling the role of RNA secondary structure in promoter-proximal pausing of RNA polymerase II in cancer cells. 

**Introduction:** Eukaryotic transcription from initiation to elongation and termination is known, whereas emerging evidence points to the pausing of transcription, in which RNA polymerase II pauses in proximal of promoter before translocating into protracted elongation. Although RNA polymerase II pausing has been shown to be a key step in transcription regulation as a rate-limiting step, the mechanisms behind this process remain poorly understood. In this study, we propose a possible mechanism in promoter-proximal pausing controlled by RNA secondary structure. Our results predicted the stability of RNA secondary structure around TSS in human genes by testing RNA free energy. Global run-on sequencing (GRO-seq) data detecting nascent RNAs were used to establish pausing possibility in the different gene regions. Then, based on the pausing possibility, we investigated the difference of RNA structural stability between those gene regions. **Results:** We identified a region downstream of the TSS that has higher RNA stability in secondary structure in comparison with gene body. By analyzing nascent RNA sequencing data, we found that highly paused genes performed higher stability and significant difference in comparison with lowly paused genes. It suggests pausing was regulated by special RNA secondary structure. Further, we used highly paused genes to characterize secondary structure elements shared among genes impacted by pausing. We found that a short stem-loop structure may contribute to RNA pol II pausing. Using its structure characteristics, we identified a substantial pausing genes in different cancer cell lines and also Drosophila cells but in different patterns. **Conclusion:** Our studies suggest that RNA secondary structure can be a temporary barrier to impede the progress of RNA polymerase II in the vicinity of transcription start sites. The structural characteristics identified in this study will provide for a way to establish pausing prediction in cells. For example, we can use pausing possibility on pausing mechanisms will contribute to understanding transcription dysregulation, thus paving the way to exploiting these insights for cancer biology.

**CPRIT Grantee Poster Session A**

**Gpr161 as a tumor suppressor in medulloblastoma**

**Introduction:** G-protein-coupled receptor, Gpr161 localizes to primary cilia, an orphan G-protein-coupled receptor, GC progenitors, and that methylates and basally represses Shh pathway in generation and maintenance of GC progenitors is unknown. **Methods:** Here, we demonstrate that neural stem cell (NSC)- or GC progenitor-specific Gpr161 knockout mice develop medulloblastomas, which are molecularly identical to Shh-subtype human tumors. **Results:** Gpr161 deletion increased Shh signaling and proliferation of GC progenitors in the external granule layer (EGL) postnatally, with highest incidence of tumorigenesis upon mid-gestational deletion in NSCs. In particular, both generation and proliferation of GC progenitors in the upper rhombic lip and formatio ependymatica, respectively, were increased in the mid-embryonic cerebellar anlage, along with upregulation of Shh signaling. Furthermore, loss of Gpr161 was accompanied by absence of cerebellar foliation, and varying degrees of dysplasia. Interestingly, concomitant disruption of cilia demonstrated to Shh-subtype medulloblastoma patients. Conclusions: Thus, Gpr161 is a bona fide tumor suppressor in Shh-subtype medulloblastoma.

**CPRIT Grantee Poster Session A**

**The possible role of PRMT1-mediated EGFR methylation in EGFR function and cetuximab sensitivity in triple negative breast cancer**

**Introduction:** We performed immunohistochemical staining of methylated EGFR at R198/200 in TNBC patient tissues. Moreover, to determine the role of PRMT1, which is the enzyme responsible for EGFR R198/200 methylation, we knocked down PRMT1 in MDA-MB-468 TNBC cells, and examined the activation of EGFR and its downstream molecules. Finally, we examined the effects of pan-PRMT inhibitor, AMI-1, on the response to cetuximab by colony formation and soft agar assays. **Results:** We found that EGFR is highly methylated as colorectal cancer, and that methylation and activity were attenuated in PRMT1-knockdown cells compared to the parental cells. We also investigated cell proliferation and sphere formation of the PRMT1-knockdown cells, and found that knockdown of PRMT1 also reduced cell proliferation and sphere formation. We also demonstrated that AMI-1 sensitized MDA-MB-468 cells to cetuximab. **Conclusions:** These results suggest that PRMT1-mediated EGFR methylation plays a role in EGFR function and cetuximab resistance in TNBC. Thus, the combination of cetuximab and PRMT1 inhibitor may be a therapeutic option for patients with methylated EGFR-expressing TNBC.

**CPRIT Grantee Poster Session B**

**MoPAC: an online tool for fast and flexible analysis of CRISPR functional screens**

**Introduction:** High-throughput functional genetic screens based on CRISPR-Cas9 screening are increasingly popular in biomedical research studies such as cancer drug discovery. CRISPR screens are diverse in experimental designs, cell types, and conditions of cell selection, making it difficult to analyze the data in “one-click.” Interactive computational tools are in demand for refined analysis and data interpretation through graphic user interfaces. **Methods:** We propose MoPAC (Modular Pipeline for Analysis of CRISPR screens), which consists of a set of optimized computational modules for quality evaluation, normalization, data interpretation, and quantitative comparison among multiple samples. Through an online graphic interface, MoPAC users are allowed to visualize their data in an interactive manner, and to define customized analysis streams that best fit the experiments. **Results:** We demonstrate the application of MoPAC in a CRISPR knockout screen on two KRAS-mutant cancer cell lines treated with MEK inhibitor. MoPAC successfully determined common and cell-specific essential genes in these lines. Moreover, it identified BRAF and FGFR1 as two key genes that are in synthetic lethality with MEK inhibition. **Conclusions:** In summary, MoPAC has shown to be a fast and flexible tool for the analysis of CRISPR functional screens, with great potential in accelerating drug discoveries.

**CPRIT Grantee Poster Session A**

**Current progress in creating an ex vivo 3D cell-culture model from decellularized mice colonos to study colorectal cancer**

**Introduction:** We performed immunohistochemical staining of human SHH-subtype medulloblastoma patients. Conclusions: Thus, Gpr161 is a bona fide tumor suppressor in Shh-subtype medulloblastoma.

**CPRIT Grantee Poster Session A**

**The possible role of PRMT1-mediated EGFR methylation in EGFR function and cetuximab sensitivity in triple negative breast cancer**

**Introduction:** We performed immunohistochemical staining of methylated EGFR at R198/200 in TNBC patient tissues. Moreover, to determine the role of PRMT1, which is the enzyme responsible for EGFR R198/200 methylation, we knocked down PRMT1 in MDA-MB-468 TNBC cells, and examined the activation of EGFR and its downstream molecules. Finally, we examined the effects of pan-PRMT inhibitor, AMI-1, on the response to cetuximab by colony formation and soft agar assays. **Results:** We found that EGFR is highly methylated as colorectal cancer, and that methylation and activity were attenuated in PRMT1-knockdown cells compared to the parental cells. We also investigated cell proliferation and sphere formation of the PRMT1-knockdown cells, and found that knockdown of PRMT1 also reduced cell proliferation and sphere formation. We also demonstrated that AMI-1 sensitized MDA-MB-468 cells to cetuximab. **Conclusions:** These results suggest that PRMT1-mediated EGFR methylation plays a role in EGFR function and cetuximab resistance in TNBC. Thus, the combination of cetuximab and PRMT1 inhibitor may be a therapeutic option for patients with methylated EGFR-expressing TNBC.
Conclusions: To more completely model the tumor microenvironment, we plan to reconstitute the matrix with human colon epithelial cells (HCEC), myofibroblasts, and adipocytes to recapitulate a more authentic niche in which the decellularization process renders the colon tissue transparent we will plan to reconstitute the matrix with human colonic epithelial cells (HCEC), then to osteoblasts, the cells from which osteosarcoma derives. We believe that it is the insufficient early-stage recruitment of chromatin binding 53BP1, and therefore its reduced retention upon double strand breaks that contribute to the HR efficiency in cells with loss of both PTEN and BRCA1. Our preliminary data also hinted that RNF168, which is molecule upstream in the DNA response pathway, is strongly associated with DBL cells and the unique gene signature of DBL group with its associated pathways analysis, we determined that the S/G2 checkpoint may be defective following DNA damage, indicating checkpoint dysregulation in this group. This observation implies that DBL cells should be sensitized to or wee1 inhibitors (e.g., MK1775) by their checkpoint defect and we’ve also further observed that DBL group exhibited significantly better sensitivity than other observed in response to MK1775. Conclusions: These data clearly demonstrate that loss of PTEN reverses HRD function in Brca1-depleted cells and this phenomenon is strongly associated with the better recruitment of Rad51 foci and less 53BP1 foci upon DSBs for DBL group, and this group can be potentially targeted by Wee1 inhibitors.

CPRIT Grantee Poster Session B

14

Bacteriophage therapy as an alternative method to treat secondary infections in cancer patients and essential importance to understand biophysical processes of DNA extraction from bacteriophages

Olgica Samoylova, The University of Texas Medical Branch at Galveston; B. Pettit

Introduction: Cancer patients during and after treatment are often at risk of getting bacterial infections. Some pathogenic bacteria develop resistance to antibiotics, which requires alternative treatment methods. Bacteriophage therapies can be used to treat such bacterial infections. There is the possibility to redesign phages to target specific bacteria strains with drug resistance. Recognition is often through the proteins of the baseplate encoded by the phage. Genetic material of bacteriophages, DNA/RNA, is transported into the cell via the baseplate and released into the bacteria, disrupting metabolism and causing the bacterium to lyse. Sequence dependent mechanical coupling of the DNA to the thermodynamics of packing can change efficiency and possibly inhibit packing of some sequences. Understanding the biophysics of the biophysical processes, which transfers a viral genome to infect a cell is very important to the cellular machinery and many disease related fields central to the sequence design issue for reprogramming phages for emerging strains. Methods: We employ all-atoms molecular dynamics simulations combined with experimental data to model DNA extraction from the bacteriophage. Different concentration of species inside the capsid and in the surrounding environment creates the osmotic pressure difference. We consider the consequences of osmotic pressure on the DNA in terms of stability and the effective interactions between DNA duplexes, salt and the environment. We use molecular dynamics simulations with semipermeable barriers to model the osmotic pressure. Results: Preliminary calculations have confirmed our implementation yields the correct osmotic pressure for ionic solutions of sodium chloride and for polyethylene glycol crowders. We performed a set of simulations designed to decompose the contributions of the osmotic pressure from the individual components (DNA, crowders, and salt) separated by semipermeable barriers. Multiple DNA molecules simulated to model DNA-DNA interactions inside the capsid were also performed. Results for the osmotic pressure are reported. Conclusions: Our approach can be used to predict the osmotic pressure necessary to confirm the presence of DNA in the system, and determine the driving force for active genome inside the viral capsid. Truncated (tail region) idealized phage systems packed with various sequences will be simulated to study the mechanical consequences with DNA transferring through the tail-channel under an external driving force. This is an integral area of research which is necessary for the development of genetically modified phages for better bacterial detection purposes or for the therapeutic applications.

15

CPRIT Grantee Poster Session A

PTEN loss confers poly [ADP-ribose] polymerase (PARP) inhibitor resistance in BRCA1-depleted triple-negative breast cancer

Jun Yin, The University of Texas M.D. Anderson Cancer Center; C. Sun; J. Garnett; C. Ip; K. Do; G. Mills; S. Lin

Introduction: BRCA1-deficient cancers, which share some similarities with TNBC in clinical pathologies and outcomes, have evolved to tolerate loss of BRCA1 function, rendering them vulnerable to PARP inhibition. Interestingly, in our preliminary data, nearly 90% (37/39) of BRCA1 low-expressing patients with BRCA1-low-gene expression also have low-level PTEN RNA levels. Patients with both low BRCA1 and PTEN gene expression levels (DBL) account for approximately 27% of the total TNBC cohort, which are associated with a worse prognosis. However, we have previously implied that cell lines with a single loss of either BRCA1 or PTEN are more sensitive to PARP inhibitors than those with loss of both, regardless of other mutations (ATM, BRCA2, or TP53). This raises the concern that PARP1 in BRCA1-deficient patients won’t be effective in those patients whose tumors simultaneously have low PTEN expression, and therefore ultimately should be treated differently. Methods: We performed global proteomic profiling (reverse phase protein array - RPPA) of MCF-10A model system before and after irradiation at different time points, aiming at finding out the key molecules that are dynamically recruited upon double strand breaks (DSBs). Additionally, by integrating transcriptome data from the selected cell lines and patients, we established a unique gene signature that was specific to DBL group, serving as a guide for targeting the pathways that are uniquely associated with DBL group. Results: We confirmed our preliminary hypothesis that the single-strand marker 53BP1, and therefore its reduced retention upon double strand breaks that contribute to the HR efficiency in cells with loss of both PTEN and BRCA1. Our preliminary data also hinted that RNF168, which is molecule upstream in the DNA response pathway, is strongly associated with DBL cells and the unique gene signature of DBL group with its associated pathways analysis, we determined that the S/G2 checkpoint may be defective following DNA damage, indicating checkpoint dysregulation in this group. This observation implies that DBL cells should be sensitized to or wee1 inhibitors (e.g., MK1775) by their checkpoint defect and we’ve also further observed that DBL group exhibited significantly better sensitivity than other observed in response to MK1775. Conclusions: These data clearly demonstrate that loss of PTEN reverses HRD function in Brca1-depleted cells and this phenomenon is strongly associated with the better recruitment of Rad51 foci and less 53BP1 foci upon DSBs for DBL group, and this group can be potentially targeted by Wee1 inhibitors.

16

CPRIT Grantee Poster Session B

Comprehensive identification of bone cancer driver genes by using Li-Fraumeni syndrome iPSCs

Strong; R. Zhao

Introduction: Osteosarcoma is one of the most frequent primary malignancies in children and adolescents. Despite the fact that the 5-year survival of localized osteosarcoma is only 60-80%, and much worse for metastatic disease, treatment strategies for this malignancy remained nearly unchanged during the last four decades. The complexity of osteosarcoma and limited access to tumor samples posed difficulties for better understanding of this disease from the molecular level. Therefore, novel and reliable disease models for osteosarcoma are in urgent need and identifying novel driver genes involved in osteosarcoma initiation and development is of great translational importance. Li-Fraumeni syndrome (LFS) is an autosomal dominant disease caused by germline mutations in the gene TP53, which predisposes individuals to a wide range of malignancies, especially osteosarcoma; thus LFS is an ideal model system to study this malignancy. We developed a novel disease model platform by reprogramming LFS patients’ fibroblasts to induced pluripotent stem cells (iPSCs), and further differentiate these iPSCs into mesenchymal stem cells (MSCs) then to osteoblasts, the cells from which osteosarcoma originate. Interestingly, LFS iPSC-derived osteoblasts recapitulate the osteosarcoma phenotype, creating “a bone tumor in a dish”. Methods: In this study, we will utilize this novel disease model to identify cancer drivers that contribute to the development of LFS associated osteosarcoma. Succinctly, we will record the genomic changes along differentiation status to confirm the “best drivers” and determine the driving force for active genome inside the viral capsid. Truncated (tail region) idealized phage systems packed with various sequences will be simulated to study the mechanical consequences with DNA transferring through the tail-channel under an external driving force. This is an integral area of research which is necessary for the development of genetically modified phages for better bacterial detection purposes or for the therapeutic applications.

CPRIT Grantee Poster Session A

Dow-Regulation of the MKK4/JNK2 Axis in NSCLC Suppresses Tumor Growth and Metastasis

Tamer Kaoud, The University of Texas Health Science Center at Houston; R. Zhou; J. Tu; A. Xu; C. Huff; L. Strong; R. Zhao

Introduction: Mitogen-activated protein kinase kinase-4 (MKK4) has been reported to either enhance or suppress oncogenic activities of its pro-oncogenic activities in breast, pancreatic, lung and skin cancer have been reported. Although the mechanism of its possible tumorigenic role is still unclear. Recent studies in glioblastoma and lung carcinoma have suggested important roles for the constitutive activation of its downstream substrate JNK2. Methods: JNKs require phosphorylation by both MKK4 and MKK7 to be fully activated. The JNK2 isoform shows a
Therefore, disruption of metabolic regulators may lead to an alteration of metabolites such as acetyl-CoA and alpha-ketoglutarate in cancer.

Introduction:

Academic research has shown that epigenome modification in leukemia-initiating-cells (LinCs) in MLL-AF9 driven leukemia. Deletion of AMPK induced multiple changes in metabolism including reducing glycolysis activity and attenuating pentose phosphate pathway. However, whether deletion of AMPK results in epigenome modification and the mechanism remains unclear. Methods: Mass spectrometry was performed to identify the altered metabolites in glycolysis. Validation of specific metabolites such as acetyl-CoA was performed using fluorometric biochemistry assays. To profile the altered epigenome in AMPK deficient LinCs, we used immunofluorescent and chromatin immunoprecipitation sequencing (ChIP-seq). Perturbation of the intracellular acetyl-CoA pool was performed by either supplementing acetyl-CoA precursor acetate to LIC culture or deleting acetyl-CoA producing enzymes such as Acy and Acs2 through the CRISPR-Cas9 system. Histone acetylation was assessed through immunoblot and cell growth was monitored by cell counting. Results: We found that acetyl-CoA levels were reduced in AMPK KO leukemia cells. Both acetylated histone H3 and H4 were decreased in AMPK KO LinCs. ChIP-Seq results indicated histone hypoacetylation across the genome as well as at MLL-AF9 targeted genes in AMPK KO LinCs. Moreover, gene set enrichment analysis revealed that the MLL-AF9 targeted gene transcripts were less enriched in AMPK KO LinCs. Lastly, we found that perturbation of the acetyl-CoA pool affected histone acetylation and cell growth. Specifically, supplementation of acetate to LIC culture increased acetyl-CoA and histone acetylation levels as well as promoting cell growth. Deleting Acs2 or Acy suppressed acetyl-CoA, decreased histone acetylation levels and hampered cell growth. Conclusions: Together, our work links AMPK to epigenomic modification and suggests that AMPK does not only serve to regulate metabolic activities. Instead, we demonstrate for the first time that AMPK regulates histone acetyl-CoA pool and further reduced histone acetylation in LICs. This resulted in suppression of MLL-AF9 targeted genes and impaired cell growth. This work raises the possibility that metabolic intervention can modify the epigenome and potentially synergize with epigenetic drugs in suppressing leukemia growth.

18

CPRIT Grantee Poster Session B

Investigating the role of the Hippo signaling pathway in mouse pancreas

Ming Gao, The University of Texas Health Science Center at San Antonio; J. Liu; F. Sharkey; R. Johnson; P. Wang

Introduction: Large tumor suppressor kinase 1 and 2 (Lats1&2) are the core kinases of the Hippo signaling pathway, and play critical roles in cell growth and organ size during animal development. Inactivation of the Hippo signaling pathway has been demonstrated to initiate tumor development in certain organs. However, the function of Lats1&2 in the pancreas and pancreatic cancer development is still elusive. Methods: To investigate the function of Lats1&2 in the pancreas, we used both adult wild-type and pancreatic acinar cell–specific deletion of Lats1&2 genes with Rosa26LSL-YFP locus. The tails of pancreata were collected for western blot and Q-PCR examination. Results: Interestingly, instead of enlarging of the pancreas or pancreatic tumors, the deletion of Lats1&2 genes (DKO) in pancreatic acinar cells resulted in severe inflammation and fibrosis of the pancreas. The pathogenesis and molecular mechanisms, we took advantage of a Rosa26 reporter to trace individual Lats1&2 null cells in vivo. We found that the loss of Lats1&2 did not affect cell growth directly but activated pancreatic stem cells (PSCs). This was followed by immune cell infiltration and acinar-to-duodenal metaplasia in Lats1&2 null pancreas. In addition, we detected that downregulated cytokines and chemokine genes, such as cTcf, cxd12, cxd16, were unregulated in Lats1&2 null pancreas before immune cell infiltration. Moreover, when we treated DKO mice with anti-cTcf antibody, we found that cTcf blockage partially rescued the pancreatitis phenotype. Finally, we revealed that deletion of Yap1 and Taz, which served as the downstream effectors of Lats1&2, can rescue the pancreatitis phenotype. Conclusions: In our present study, we found that deletion of the Lats1&2 genes in acinar cells caused pancreatitis through activation of pancreatic stem cells. Our study discovered a new mechanism of the inflammatory and fibrotic response initiated by pancreatic epithelial cells and partially resolved the enigmatic role of the Hippo signaling pathway, which is likely to be useful for the identification of new strategies for controlling pancreatic inflammation and fibrosis, as well as prevention of pancreatic cancer. Acknowledgement: Ming Gao is supported by pre-doctoral fellowship through CPRIT Research Training Award RP 170345. *Jun Liu was supported by a post-doctoral fellowship through CPRIT Research Training Award RP140105. *Pei Wang is CPRIT scholar and funded by First time faculty award.

19

CPRIT Grantee Poster Session B

A AMP-activated protein kinase links metabolic regulation to epigenome modification in leukemia-initiating-cells

Yajian Jiang, Baylor College of Medicine; A. Kitanos, V. Luu; T. H.; D. Nakada

Introduction: Metabolic reprogramming impinges on epigenome through metabolites such as acetyl-CoA and alpha-ketoglutarate in cancer. Therefore, disruption of metabolic regulators may lead to an alteration of the epigenome. AMP-activated kinase (AMPK) is a master regulator of energy homeostasis by activating catabolic pathways and suppressing anabolic activities. Previously we found that AMPK is essential for the leukemogenic function of leukemia-initiating-cells (LICs) in MLL-AF9 driven leukemia. Deletion of AMPK induced multiple changes in metabolism including reducing glycolysis activity and attenuating pentose phosphate pathway. However, whether deletion of AMPK results in epigenomic modification and the mechanism remains unclear. Methods: Mass spectrometry was performed to identify the altered metabolites in glycolysis. Validation of specific metabolites such as acetyl-CoA was performed using fluorometric biochemistry assays. To profile the altered epigenome in AMPK deficient LICs, we used immunofluorescent and chromatin immunoprecipitation sequencing (ChIP-seq). Perturbation of the intracellular acetyl-CoA pool was performed by either supplementing acetyl-CoA precursor acetate to LIC culture or deleting acetyl-CoA producing enzymes such as Acy and Acs2 through the CRISPR-Cas9 system. Histone acetylation was assessed through immunoblot and cell growth was monitored by cell counting. Results: We found that acetyl-CoA levels were reduced in AMPK KO leukemia cells. Both acetylated histone H3 and H4 were decreased in AMPK KO LICs. ChIP-Seq results indicated histone hypoacetylation across the genome as well as at MLL-AF9 targeted genes in AMPK KO LICs. Moreover, gene set enrichment analysis revealed that the MLL-AF9 targeted gene transcripts were less enriched in AMPK KO LICs. Lastly, we found that perturbation of the acetyl-CoA pool affected histone acetylation and cell growth. Specifically, supplementation of acetate to LIC culture increased acetyl-CoA and histone acetylation levels as well as promoting cell growth. Deleting Acs2 or Acy suppressed acetyl-CoA, decreased histone acetylation levels and hampered cell growth. Conclusions: Together, our work links AMPK to epigenomic modification and suggests that AMPK does not only serve to regulate metabolic activities. Instead, we demonstrate for the first time that AMPK regulates histone acetyl-CoA pool and further reduced histone acetylation in LICs. This resulted in suppression of MLL-AF9 targeted genes and impaired cell growth. This work raises the possibility that metabolic intervention can modify the epigenome and potentially synergize with epigenetic drugs in suppressing leukemia growth.

20

CPRIT Grantee Poster Session B

Critical Role of NLRP12 in Colorectal Cancer

Hakan Zaki, The University of Texas Southwestern Medical Center; S. Hu; Y. Kwak

Introduction: NLRP12, a cytosolic pattern recognition receptor in the family of NOD-like receptors, has recently emerged as negative regulator of intestinal inflammation and cancer. We have demonstrated that Nlrp12-/ mice are highly susceptible to azoxymethane (AOM) plus dextran sodium sulfate (DSS)-induced colorectal cancer (CRC), showing increased tumor burden and faster tumor progression. However, the precise role of NLRP12 in the regulation of the Wnt/b-catenin pathway remains unclear. Therefore, here we investigated the molecular mechanism of NLRP12-mediated regulation of colorectal cancer using a chemical injury models (AOM/DSS) and genetic models (APCmin+) model. Methods: To understand the role of NLRP12 in CRC, we induced colorectal tumorigenesis in wild-type and Nlrp12-/- mice using AOM plus DSS. Colon tissue collected at day 10 and day 80 following tumor induction was analyzed for the activation of cell signaling pathways and the expression of pro-tumorigenic molecules. In a different approach, we crossed WT and Nlrp12-/- mice with Apcmin mice. Apcmin and Apcmin/Nlrp12-/- mice were examined for the development of intestinal and colonic polyps at 5 months after birth. Tumor burden were counted, cell signaling pathways were analyzed by western blotting, and the expression of tumor promoting factors were measured by real time PCR. Results: While we observed increased activation of inflammatory signaling pathways NF-B and ERK in the colon of Nlrp12-/- mice, we did not observe such effect of NLRP12 on NF-B and ERK was observed in tumors (day 80). In contrast, tumor bearing colons of Nlrp12-/- mice express higher level of tumorigenic factors including cMyc, Axin2, Ccd1, Cox2, Lgr5, and Vinculin when compared to those in WT mice. Interestingly, these genes are downstream of the Wnt/b-catenin signaling pathway. Consistently, AOM/DSS-treated Nlrp12-/- mouse colonies exhibit significantly elevated levels of -catenin. The role of NLRP12 in the regulation of the Wnt/b-catenin pathway was further evidenced by studies using Apcmin mice. Crossing Nlrp12-/- mice with Apcmin mice leads to a remarkable delay in colon polyps development in the small and large intestines. We also observed higher expression of tumor promoting genes in Nlrp12-/-Apcmin mouse colonies as compared to those in Apcmin mice. Conclusions: Our data suggest that NLRP12 may play a role in regulating CRC via regulation of the Wnt/b-catenin signaling pathway.
21 CRPRIT Grantee Poster Session A Developing therapeutic strategies for lung cancer treatment by targeting mitochondrial function Sarada Preeta Kalainayakan, The University of Texas at Dallas; P. Ghosh; S. Dey; K. FitzGerald; L. Liu; L. Zhang

Introduction: Preliminary studies focused mainly on the precept that tumors depend on glycolysis for energy and growth (the Warburg effect) and that mitochondria are dysfunctional in cancer cells. However, there is mounting evidence suggesting that some cancer cells exhibit enhanced mitochondrial respiration. Recent studies in our lab have demonstrated that non-small cell lung cancer (NSCLC) cells exhibit intensified mitochondrial respiration and oxygen consumption. We further demonstrated that targeting increased mitochondrial respiration with a therapeutic agent that causes enhanced ROS production and mitochondrial fission effectively hampers proliferation of NSCLC cells in vitro. Our study aims to determine whether targeting mitochondrial function affects NSCLC tumor growth and progression in vivo. Methods: Luciferase expressing NSCLC cells were implanted in the lungs of NOD/SCID mice to generate orthotopic xenografts. The mice bearing orthotopically implanted NSCLC tumors were treated with an agent that targets mitochondrial function. Tumor growth was monitored by non-invasive bioluminescence imaging (BLI). Immunohistochemistry (IHC) was performed on sections obtained from paraffin embedded lung tissues to discern the mechanisms of action of the agent. Results: BLI data demonstrated that there was a considerable reduction in radiance in mice that received the mitochondria-targeting agent. IHC data indicated that there was a reduction in expression of proteins involved in heme transport and degradation and hemoproteins involved in mitochondrial respiration in mice treated with the mitochondria-targeting agent. Further, IHC data indicated reduced levels of a putative heme sensor and heme chaperone necessary for maintaining levels of cellular heme and hemoproteins in mice that received the mitochondria-targeting agent. Conclusions: Our results suggest that targeting mitochondrial dysfunction in tumor cells results in the inhibition of tumor growth and significantly inhibiting lung tumor growth. Our results also indicate the possibility that our mitochondria targeting agent acts via regulating levels of a putative heme sensor.

22 CRPRIT Grantee Poster Session B Targeting the Epigenetic Vulnerabilities of Myeloid Leukemia Jian Xu, The University of Texas Southwestern Medical Center; Z. Gu; Y. Liu; H. Cao; M. Chen; Y. Zhang; L. Qi; X. Li; K. Li; K. Dickerson; F. Cai; W. Chen; M. N.; R. DeBardelandy

Introduction: Myeloproliferative neoplasms (MPNs) are clonal, progressive cancers characterized by alterations of multiple signaling pathways, including JAK2, RAS and EP www.EZH2-mutant mice. Our original hypothesis was that E2-KO affecting Ezh2 expression in mouse hematopoietic stem/progenitor compartments and a skewed differentiation towards early lethality. These mice also displayed expansion of hematopoietic progenitor and CD34+ cells, severe anemia, extramedullary hematopoiesis, and megakaryopoiesis at the expense of erythropoiesis in the bone marrow and spleen. More importantly, while no fibrosis was observed in NRasG12D+/− mice, loss of Ezh2 together with NRasG12D+/− (E2-KO) resulted in extensive myelofibrosis, destructive myelodysplasia, and occasional leukemic infiltration in the bone marrow, spleen and liver. Our results provide compelling genetic evidence that Ezh2 insufficiency and oncogenic Ras contribute synergistically to the development of MPNs, particularly myelofibrosis. Strikingly, while loss of Ezh1 alone did not cause any defects in normal hematopoiesis, concurrent inactivation of Ezh1 and Ezh2 (E1E2-KO) completely abolished MPN development and myelofibrosis. Conclusions: Our results established an essential role of Ezh1 in the pathogenesis of Ezh2-deficient MPNs, and identified a selective epigenetic vulnerability for MPNs induced by Ezh2 deficiency. The selective vulnerabilities raise the possibility of leveraging Ezh2 as targets for epigenetic therapies to specifically eradicate Ezh2-mutant tumors. Our study promises to provide critical insights into developing new therapies to selectively eliminate leukemia-initiating cells harboring alterations of epigenetic pathways.

23 CRPRIT Grantee Poster Session A Intratumour Heterogeneity is Associated with Survival of Patients with Stage IA Lung Adenocarcinoma Kelly Quek, The University of Texas M.D. Anderson Cancer Center; J. Li; J. Fujimoto; J. Zhang; J. Wang; W. Lee; R. Chen; C. Chow; C. Behrens; X. Ma; A. Cornea; X. Song; J. Zhang; E. Roarty; R. Thornton; M. Coyle; L. Little; C. Gumbs; M. Antonoff; N. Kalhor; C. Moran; A. Weissferdt; W. William Jr.; S. Swisher; J. Lee; J. Heymach; I. Wistuba; P. Futreal; J. Zhang

Introduction: Our previous study has suggested that complex genomic intratumour heterogeneity (gITH) was associated with an increased risk of relapse in patients with localized lung adenocarcinomas (LUAD). We have launched a study to investigate genomics profile ITH of Stage IA NSCLC (a patient population with no optimal biomarker to guide post-surgical therapy) to understand the molecular evolution during early carcinogenesis and to identify biomarkers for early detection and intervention. Methods: We performed multiregion whole exome sequencing on 30 Stage IA LUAD and 10 normal lung tissue samples from a median sequencing depth of 49x. 15 patients have relapsed within 3 years post-surgery (cases) and 15 patients have not relapsed with a minimum of 5-year post-surgical follow up (controls). Shannon diversity index (SDI) was used to quantify ITH in individual tumors. Kaplan-Meier method was used to evaluate the relationship between ITH and disease-free survival (DFS) as well as overall survival (OS). Results: Consistent with our previous study, 22 of 24 (91.7%) canonical cancer gene mutations were shared events by all regions of individual tumour. Compared to non-relapsed controls, tumours from relapsed cases demonstrated significantly higher degree of ITH (mean average SDI of 1.43 in cases versus 1.21 in controls, p = 0.03 and mean maximum pairwise SDI of 1.84 in cases versus 1.62 in controls, p = 0.008). Compared to non-relapsed controls, tumours from relapsed cases demonstrated significantly higher degree of ITH (mean average SDI of 1.43 in cases versus 1.21 in controls, p = 0.03 and mean maximum pairwise SDI of 1.84 in cases versus 1.62 in controls, p = 0.008). Higher degree of gITH was associated with shorter OS (p = 0.003) and shorter DFS (p = 0.004). Significantly higher mutation burden was observed in tumors from relapsed patients (average 10.4 mutations per Mb versus 6.94 mutations per Mb, p = 0.03). The overall survival data has shown strong enrichment of signature 4 substitutions (associated with smoking) and a subtle degree of enrichment for signature 1 (associated with age), and signature 13 (associated with APOBEC), reflecting multiple mutational processes contributing to the genetic diversity during cancer development. Conclusions: Majority of cancer mutations are clonal events during early carcinogenesis of LUAD. Complex gITH may be associated with more aggressive biology and inferior clinical outcome with Stage IA LUAD, therefore, may be evaluated as a potential biomarker.

24 CRPRIT Grantee Poster Session B Pancreatic ductal adenocarcinoma can be generated from human acinar cells Pai Wang, The University of Texas Health Science Center at San Antonio; J. Liu; N. Akunma

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadly human malignancies and is characterized by the accumulation of a series of genetic mutations during disease progression. Few models are available to study the molecular mechanisms of the tumorigenesis process of human PDAC. Methods: To model human PDAC development, we developed a genetic manipulation system to transduce normal human primary pancreatic exocrine cells (hPECs) with lentiviral vector expressing KRASG12D-mCherry and lentiviral CRISPR targeting CDKN2A/p16, p53 and SMAD4. We have confirmed the efficiency of the p16 CRISPR, p53 CRISPR, and SMAD4 CRISPR constructs by editing the genome to mutate the respective gene loci. We identified the signaling pathway that promotes acinar to ductal metaplasia (ADM) from hPECs. To generate PDAC from hPECs, we sorted acinar cells from hPECs and induced ADM. Two million of the genetically engineered AD cells were transplanted subcutaneously or orthotopically into NOD/SCID mice. Results: The xenografts were harvested two months after transplantation. Pathological analysis found that invasive and metastatic PDAC were generated. We confirmed that the xenografts are derived from human cells with anti-human nuclear antigen antibody (anti-HuNu). Anti-Fan cytokeratin staining proved that the lesions were made up of epithelial cells. Conclusions: For the first time, we have generated PDAC from human acinar cells, suggesting acinar cells are one of the origins for
PDAC. Further comparison with ductal cell derived tumors is ongoing. Our study will reveal the cellular origins of PDAC and provide insight into human PDAC development.

25  
**CPRIT Grantee Poster Session A**

**FGF-WNT cooperativity and the novel role of IncRNAs in translational regulation in breast cancer: a new SINE of the times**

Yu Qi; L. Xiao; X. Hu; J. Wang; K. Cui; J. Yuan; B. Zhang; J. Zhang; L. Zhao; Z. Li; Y. Han; L. Sun; J. Liu; Z. Liu; W. Li; H. Huang; X. Wang; X. Zhao; C. Liu; Z. Sun; D. Zhao; S. Sun; Y. Feng; H. Gao; Z. Jia; Z. Bai; J. Zhang; M. Li; K. Lu; H. Wang; Y. Xu; Y. Li

**Introduction:** FGF and WNT signaling are frequently deregulated in human cancer and play critical roles in mammary stem cell self-renewal and expansion. Breast tumors with deregulation of both pathways have the worst prognosis compared with those with deregulation of either pathway alone. Using an inducible system of FGFR1 (iFGFR1), we demonstrated that simultaneous activation of FGF and WNT signaling dramatically reduces tumor latency as compared to activation of either pathway alone. The resulting tumors exhibit increased expression of critical translation machinery components, indicating potential involvement of translational regulation in FGF-WNT induced tumorigenesis. In this study, we investigated the translational mechanisms and propose a novel role of long non-coding RNAs (IncRNAs) in regulation of translation. **Methods:** We employed ribosome profiling (ribo-seq) to identify selectively translated mRNAs (residues +1, +2, and +3) and identified by acute iFGFR1 activation and ribosome profiling (iFGFR1 + ribo-seq), with expression and ribosomal occupancy in epithelial cells with constitutive WNT hyperactivation. RNA-Seq and mass spectrometry were performed for inter-omic correlation analyses. CRISPR-Cas9 technology was utilized to test regulatory roles of IncRNAs in translation. **Results:** Many genes involved in mitosis and stem cell signaling pathways were translationally upregulated upon iFGFR1 activation while many genes with decreased translation are involved in senescence. Transcripts with enhanced translation are enriched for G-quadruplex and poly-U motifs at the 5' and 3' UTR respectively. Treatment with Silvestrol, an inhibitor of eIF4A, a protein required for unwinding G-quadruplexes to initiate translation, delays FGF-WNT induced tumor progression without affecting mouse weight, suggesting the therapeutic potential of translational inhibitors in FGF-WNT tumorigenesis. In addition to mRNAs, many IncRNAs are associated with ribosome profiling and correlated affinely with iFGFR1 activation, implicating potential roles of IncRNAs in translational regulation. Surprisingly, Malat1, originally thought to be a nuclear-restricted IncRNA that regulates metastasis, has increased affinity for polysomes upon iFGFR1 activation. We demonstrated that Malat1 transcribes localize to the nucleus in cell cycle dependent manner, which can be regulated by iFGFR1 signaling. Through bioinformatics analyses, we identified 123 mRNAs that may base pair with the SINE element, which is about 100 base pairs on Malat1. Deletion of the SINE element resulted in an inhibition of cell proliferation, G1 arrest, mitotic defects, and more surprisingly decreased ribosomal occupancy. **Conclusions:** The mechanism of crosstalk between IncRNAs and translational regulation in FGF-WNT driven cancer progression, specifically how Malat1 regulates protein synthesis.

26  
**CPRIT Grantee Poster Session B**

**Structural Study of Regulation of de novo DNA Methyltransferases**

Ran Ren; The University of Texas M.D. Anderson Cancer Center; X. Zhang; X. Cheng

**Introduction:** DNA methylation is an important epigenetic modification for regulation of gene expression and chromatin organization. De novo DNA methyltransferases Dnmt3a and Dnmt3b, together Dnmt3L, established genomic DNA methylation pattern during embryonic and germ line development, with DNMT3L3 as an accessory factor. Dnmt3a and Dnmt3b have more than thirty isoforms from alternative splicing diverging family of DNA binding transcription regulators in mammals. Dnmt3b is frequently overexpressed in cancer cells. It has recently been shown that Dnmt3b appears to be able to stimulate gene body methylation in differentiated cells, whether Dnmt3a and Dnmt3b enzymatic activities are regulated and (if so) the structural basis for that regulation. Our data lead to a model in which a catalytic inactive Dnmt3b recruits Dnmt3a and -3b to regions of chromatin where epigenetic modifications occur.

27  
**CPRIT Grantee Poster Session A**

**Xenotransplantation of pediatric low grade gliomas confirms the enrichment of BRAF V600E mutation and preservation of CDKN2A deletion in a novel orthotopic xenograft mouse model of progressive pediatric brain tumors.**

K. Jia; S. Chen; J. Ding; M. Huang; M. Wang; Y. Liu; J. Ren; J. Tran; J. Murray; P. Baxter; X. Yuan; J. Su; A. Adesina; L. Perlaky; M. Chintagumpala; D. Parsons; C. Lau; S. Yeh; X. Xu; L. Li

**Introduction:** Pediatric low grade gliomas (PLGG) may still recur despite gross total resection. To identify cellular and molecular changes that drive PLGG progression, we analyzed putative cancer stem cells (CSCs) and evaluated key biological changes in a novel and progressive patient-derived orthotopic xenograft (PDOX) mouse model. **Methods:** 6 PLGGs were collected and examined for putative CSC (CD133 and CD10+ Subpopulation in SCID mouse models. Long-term in vivo evolution was analyzed in a novel PDOX model of pleomorphic xanthoastrocytoma (PXA), named IC-3635PXA. Reproducibility of histological features of original patient tumor, progressive phenotype and neural stem cell brain rearrangement remains consistent. Genetic alterations (BRAF V600E and CDKN2A) were confirmed by pyrosequencing and FISH, respectively. In vitro drug screening for BRAF V600E inhibitors and BRAF inhibitors was performed with xenograft-derived 3635PXA cell line. **Results:** Flow cytometric analysis of 22 PLGGs detected CD133+ (>1.5%) and CD15+ (20.7 ± 28.9 %) cells, and direct intra-cranial implantation of 25 PLGGs led to the development of 1 PDOX model from a grade II PXA. While CSC levels did not correlate with patient tumor progression, neurosphere formation and in vivo tumorigenicity, the PDOX model, IC-3635PXA, reproduced key histological features of the original tumor. Similar to the patient tumor that progressed and recurred, IC-3635PXA also progressed during serial in vivo subtransplantations (4 passages), exhibiting increased tumor take rate, elevated proliferation, loss of mature glial marker (GFAP), accumulation of GFAP-Vimentin+ cells, enhanced local invasion, distant perivascular migration, and prominent reactive gliosis in normal mouse brains. Molecularly, xenograft cells with homozygous deletion of CDKN2A shifted from disomy chromosome 9 to trisomy chromosome 9; and BRAF V600E mutation allele frequency increased (from 28% in patient tumor to 67% in passage III xenografts). In vitro drug screening identified 2/7 BRAF V600E inhibitors and 2/9 BRAF inhibitors with suppression of cell proliferation. In summary, we showed that PLGG tumorigenicity was low despite the presence of putative CSCs, and our data supported GFAP-Vimentin+ cells, CDKN2A homozygous deletion in trisomy chromosome 9 cells, and BRAF V600E mutation as candidate drivers of tumor progression in the PXA xenografts.

28  
**CPRIT Grantee Poster Session B**

**Structural and Functional Study of Transcriptional Repressive Complex of KAP1/Trim28 with KRAB Domain containing Zinc Finger proteins**

Suparna Bhattacharya; The University of Texas M.D. Anderson Cancer Center; Suparna Bhattacharya; The University of Texas M.D. Anderson Cancer Center; Z. Zhou; X. Zhang; Z. Wang; X. Cheng

**Introduction:** Krüppel-associated box (KRAB) domain containing Cys2–His2 (C2H2) zinc finger (ZF) proteins are the largest and most rapidly diverging family of DNA binding transcription regulators in mammals (1). KRAB-ZF proteins act mostly as transcriptional repressors (2) via KRAB associated recruitment of the corepressor protein KAP1 (3), also known as Kruppel-like protein 5 (KLF5). The C2H2 protein complexes (8) and their KRAB domain (3). **Methods:** We developed a co-expression and co-purification scheme of KAP1/Trim28 with KRAB domain of ZF proteins (5). **Results:** We developed a co-expression and co-purification scheme of KAP1/Trim28 proteins in complex with KRAB domain of ZF proteins (5). **Conclusions:** We showed that the catalytic inactive Dnmt3b can form stable complex with Dnmt3a and Dnmt3b and influence their enzymatic activity, similar to Dnmt3L. We are characterizing these complexes structurally to understand the mechanism how Dnmt3b stimulates the activity of Dnmt3a and Dnmt3b.
mice with CDX2-Cre mice to generate Apc580mu-PPARD-KO-Gut mice, in which PPARD genetic deletion and APCFS0 mutation were intestinally targeted via Cre-recombinase expression driven by the CDX2 promoter. 

Results: PPARD KO in intestine of Apc580mu-PPARD-KO mice was verified by qRT-PCR and western blot. PPARD deletion significantly reduced tumor numbers in both colon and 1/3 distal small intestine in Apc580mu mice and prolonged survival of the mice with Apc580mu from 213.5 ± 3.9 days for the mice with WT PPARD to 200.00 ± 10.45 days for the mice with intestinal PPARD KO. PPARD KO significantly reduced the colonic crypt proliferative zone in Apc580mu mice, as demonstrated by Ki67 immunohistochemistry staining. Furthermore, PPARD KO decreased the levels of active β-catenin and its downstream gene cyclin D1 in colorectal epithelial cells of Apc580mu mice, as measured by western blot and q-RT-PCR, respectively. 

Conclusions: Our findings demonstrate the mechanistic importance of PPARD to CRC tumorigenesis as driven by APC mutations.

31

CPRIT Grantee Poster Session A
Dynamic Regulation of Histone Acetylation by Nuclear Proteolysis Controls Cell Cycle Gene Expression and Chromosome Integrity in Multiple Myeloma
Laure Manex; Baylor College of Medicine; P. Iakovova; S. Moree; L. Fletcher; F. Lolla; S. Yeltapragada; A. Catic

Introduction: Transcription factors are generally short-lived proteins that are crucial for active transcription. The dynamic interaction of transcription factors and co-regulators allows cells to continuously adjust gene expression. Whereas the composition and binding of transcription factors at genomic sites is the focus of a widespread research effort, relatively little is known about how these proteins are being removed by the ubiquitin-proteasome system (UPS). Multiple myeloma (MM), the second most common hematopoietic malignancy, has become a model disease for drugs that interfere with the UPS through either blocking or facilitating protein degradation. The proteasome inhibitor Bortezomib, for instance, is used as first-line treatment in myeloma; yet, the process by which myeloma cells are killed by this drug is ill-defined. Since transcription factors are prime targets of proteasomal degradation, our research is focused on defining how proteolysis regulates transcriptional dynamics in this disease and determining the therapeutic relevance for treatment strategies that directly target the UPS to the disease. 

Methods: Following proteasome inhibition in multiple myeloma cell lines, we performed chromatin-immunoprecipitation for histone H3 acetylation (K27) and multiple histone deacetylases and used next generation sequencing (ChIP-seq) to identify unique gene clusters that are actively regulated by the proteasome and quantify epigenetic changes in dependence of proteasome inhibitors. 

Results: Our findings reveal that cell cycle genes, particularly subsets of genes involved in centromere formation and sister chromatid segregation during mitosis, are associated with nuclear protein turnover and are transcriptionally repressed by proteasome inhibition. Notably, proteasome inhibition increased the recruitment of specific histone deacetylases (HDACs) to the promoters of genes involved in centromere formation. We are investigating the mechanisms for UPS regulation of HDAC abundance at specific genomic loci. Moreover, data analysis of a panel of multiple myeloma patients shows that the expression levels of HDACs correlate with patient survival, as well as clinical characteristics of disease. We are currently exploring how histone modifications and proteasome activity crosstalk in a therapeutically relevant manner in multiple myeloma. 

Conclusions: This research project will contribute to our understanding of epigenetic and transcriptional dynamics in MM. With our focus on the continuously changing abundance of transcription factors and co-regulators at promoter sites, we seek to unlock new pathways for molecular therapy, as well as identify more specific targets for advance treatment compared to blunt proteasome inhibition. Elucidating the mechanisms of action and resistance to proteasome inhibition will help advance future MM therapy.

32

CPRIT Grantee Poster Session B
Effects of TLX/NE21 ligands on gene expression in Glioblastoma cell line
Alessandra Cyroro; Houston Methodist; C. Benod; D. Siegal; P. James; P. Webb; H. Pownall

Introduction: The nuclear receptor (NR) superfamily consists of transcriptional factors that are highly attractive targets for addressing a range of pathologies including cancer. In addition to the well-characterized ligand-activated NRs, this family comprises a large number of orphan nuclear receptors (ONRs) that remains uncharacterized. A large subset of the NRs, known as orphan nuclear receptors (ONRs), are predominantly expressed in the central nervous system. TLX is highly expressed in Glioblastoma Multiforme (GBM) and drives neural stem cells (NSC) and brain tumor stem cells (BTSC) self-renewal; these qualities make TLX a potential therapeutic target for treating GBM. We recently identified multiple TLX ligands that potentiate its repressive activity. Now, we have identified new binding compounds with therapeutic promise.
**Cancer Biology**

Understanding how ligands regulate transcriptional activity is critical to the development of more efficient and selective anti-cancer drugs. **Methods:** We assessed effects of five TLX ligands (published compounds cpr1, cpr2, cpr3 and new compounds IACS-809 and IACS-814) in glioblastoma cell line LN229 using the Illumina BeadArray. Results were verified by qRT-PCR. Pathway Enrichment Analysis was performed using GeneCodis analysis. **Results:** Microarray analysis to compare TLX ligands influenced expression of multiple genes. VEGF, the cell membrane associated transcription factor, was upregulated an average of 12.8-fold over WT MYOD1, and using RTPCR to confirm "exon 2 skipping". **Conclusions:** Our findings indicate that the recruitment of CRM1/UGF1 to chromatin leads to DNA hypomethylation in cancer.

**35**

**CPRIT Grantee Poster Session A**

**Discovery of Novel Transcript Variants of Myogenic Regulatory Factors in Rhabdomyosarcoma**

**Erin Butler, The University of Texas Southwestern Medical Center; Y. Zheng; L. Xu; S. Skapek**

**Introduction:** Rhabdomyosarcoma, the most common soft tissue sarcoma in children, is composed of skeletal myoblast-like cells in which normal differentiation programs – including an irreversible cell cycle arrest – are seemingly derailed. The molecular basis for the differentiation arrest are not clear in most cases of rhabdomyosarcoma. Given the apparent differentiation arrest, we hypothesized that alternative splicing in the MYOD1 family of muscle regulatory factors contribute to the differentiation defect in rhabdomyosarcoma, providing a selective growth advantage to incipient rhabdomyosarcoma cells. **Methods:** A computational algorithm was used to detect alternative splicing in myogenic regulator factors using RNAseq data from 44 rhabdomyosarcoma specimens. Retroviral vectors were generated to express wild type (WT) and splicing variants, and GFP or RFP markers, in cultured fibroblasts and human rhabdomyosarcoma cells, and the effects were analyzed using a variety of molecular and cell biology approaches. **Results:** Of genes encoding the four MYOD1-related muscle differentiation factors (MYOD1, MYF5, MYOG, MRF4), RNAseq analysis showed evidence for alternative splicing to "skip" exon 2 in only MYOD1 and MYF5 in 34% and 38% of RMS specimens but not in normal human muscle. RTPCR demonstrated the presence the alternatively spliced form of MYOD1, MyoDdelta-exon2, in two rhabdomyosarcoma cell lines. Ectopic expression of WT MyoD, but not MyoDdelta-exon2, induced morphologic changes and muscle gene expression in cultured fibroblasts and Rh18 rhabdomyosarcoma cells. By using GFP and RFP markers, competitive co-culture assays demonstrated a growth advantage to fibroblasts expressing MyoDdelta-exon2. **Conclusions:** Alternative splicing in rhabdomyosarcoma can generate forms of MYOD1 and MYF5 that lack exon 2, rendering them unable to foster muscle differentiation and the accompanying cell proliferation arrest. **40**

**CPRIT Grantee Poster Session A**

**Mediator Kinase as a transducer and therapeutic target in oncogenic WNT/B-Catenin signaling**

**Lindsey Barron, The University of Texas Health Science Center at San Antonio; A. Clark; T. Boyer**

**Introduction:** Colorectal cancer (CRC) remains a major health problem worldwide, with the incidence highest in developed countries, especially among men and women. Recently, colorectal cancer (CRC) arises from the maintenance of the progenitor phenotype in intestinal crypts, which is dependent on the expression of genes programmed by the canonical WNT/beta-catenin pathway. Accordingly, constitutive pathway activation through mutations in the Adenomatous
Polyposis Coli (APC) tumor suppressor or B-catenin is a driver in >90% of CRCs. B-catenin activates transcription through its direct physical and functional interaction with the Med12 subunit of Mediator. Wilson Mediator, Med12 nucleates the assembly of a discrete “kinase” module that includes Med13, Cyclin C, and CDK6, an oncrogenic protein required for B-catenin-dependent gene activation and CRC growth. These findings establish the Mediator kinase module as a key node of oncogenic activation within the WNT/B-catenin pathway, and further identify CDK6 kinase activity as a prospective therapeutic target in WNT-driven CRCs. Mechanistically, B-catenin binds directly to Med12 within the kinase module, triggering Med12-dependent activation of CDK6 through a direct interaction involving Med12 exon 2-encoded sequences and a phylogenetically conserved surface groove on Cyclin C. In this study, the CRISPR/Cas9 system was used to abrogate Mediator kinase activity by genetic disruption of the Med12:Cyclin C interface in the human CRC cell line, HCT116. ChiP-seq for H3K27ac was used to determine superenhancer alterations. Global levels of H3K27ac and H3S10P were assessed by immunoblot. Results: Loss of Mediator kinase activity altered the epigenetic deposition of the active superenhancer mark, H3K27ac, and lead to diminished expression of WNT-target genes, reduced cell proliferation and colony formation. Globally, levels of the H3K27ac mark correlate with the H3S10P mark, which has been previously shown to be CDK6-dependent. Conclusions: Therefore, we conclude that the Mediator kinase module plays a role in regulating superenhancer integrity via the deposition of the H3K27ac and H3S10P mark. Since genetic disruption of the Med12:Cyclin C interface reverses the oncogenic properties associated with these marks, we believe that this point represents an attractive target for the development of targeted molecular therapies for advanced stage CRC. Lindsey Barron is supported by a CPRIT postdoctoral training fellowship, the CPRIT Research Training Award (RP170345).

37 CPRIT Grantee Poster Session A

Data mining immune repertoires in cancer tissue biopsy Jared Ostmeyer, The University of Texas Southwestern Medical Center; S. Chrisly; W. Rounds; I. Toby; B. Greenberg; N. Monson; L. Cowell

Introduction: Tumor infiltrating lymphocytes (TILs) can be found in tumor biopsies from different tumor types, and the proportion of a tumor, are often suppressed by the tumor microenvironment. With the advent of next generation sequencing, it has become possible to sequence several thousand unique immune receptor sequences per tumor biopsy. However, identifying which sequences are important has proven challenging because only a subset of the immune receptors are likely participants in the anti-tumor immune response—the other immune receptors represent irrelevant noise. Methods: Immune receptor sequences from cancer biopsies are downloaded from publicly available databases. Statistical methods we developed are used to identify receptor sequence features. We have developed a family of statistical methods to help identify immune receptors that are in response to a specific disease. Every receptor sequence is scored by a detector function, and the scores are aggregated together to predict a sample label. The detector function is found by maximizing the area under the ROC curve. Results: We have developed new methods to help identify tumor infiltrating lymphocytes responsible for anti-tumor immune response. These receptors might serve as the basis for new kinds of therapies.

38 CPRIT Grantee Poster Session B

Playing at the ‘NET’ benefits breast cancer metastasis Arzu Ulu, The University of Texas Health Science Center at Houston; J. Frost

Introduction: Breast cancer is a deadly disease affecting 1 in 8 women in the United States. The 5-year survival in patients with metastatic disease is only 22% despite huge efforts at early detection and improved treatment options. Here, we review our efforts in understanding the molecular mechanisms associated with the metastatic phenotype. Cancer cells need to gain migratory and invasive properties to metastasize to distant sites. Activation of the RhoGTPase network, RhoA, is critical for cancer cell migration and invasion, and RhoA is overexpressed in breast cancer. Unfortunately, direct targeting of RhoGTPases is challenging due to their drug-resistant, nucleotide binding site and ubiquitous expression which underscores the necessity of finding different targets that would interfere with the RhoGTPase pathway. Methods: For this reason we have used tools to identify drug targets that can potentially interfere with the RhoA network. Our approach involves interfering with a ‘NET’ that has been shown as undruggable, we focused on its unique modulator, the RhoGEF Net1A (neurepithelial cell transforming gene 1A). We employed immunofluorescence staining, cell migration and invasion assays to elucidate how Net1A controls RhoA activation and cell motility. Results: While other RhoGEFs are exclusively in the cytosolic compartment of cells, Net1A localizes to the nucleus in the absence of stimulation, preventing it from activating RhoA. Upon stimulation of breast cancer cells with EGF (epidermal growth factor), Net1A relocates into the cytosol and activates RhoA, which in turn promotes cell migration and invasion. We demonstrated that the RhoGEF PK (mitogen activated protein kinases) pathway, as well as CRM1 (chromosomal maintenance 1)-mediated nuclear export are involved in EGF-induced cytosolic relocalization of Net1A in breast cancer cells. Conclusions: Using an innovative approach by focusing on a unique RhoA modulator, our study identifies a novel mechanism for controlling cell migration and invasion, which subsequently highlights novel anti-cancer targets. Since there are inhibitors for these targets currently in clinical trials, this study will progress fast towards conducting in vivo experiments and more importantly human trials. Acknowledgement: UTHHealth Innovation for Cancer Prevention Research Training Program-Post-Doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP160015).

39 CPRIT Grantee Poster Session A

In vivo analysis reveals temporally and spatially distinct homologous recombination pathways and a potential chemotherapeutic target Rhea Kang, The University of Texas M.D. Anderson Cancer Center; F. Cole; M. Biot

Introduction: Homologous recombination (HR) faithfully repairs DNA double-strand breaks (DSBs) and contains many semi-redundant pathways, but our knowledge of which HR repair pathways are used under which condition is limited, especially in vivo at endogenous sites. Meiotic recombination is an excellent system to study HR because a large number of programmed DSBs are repaired by HR using the homologous chromosome, which allows us to track natural outcomes at endogenous hotspots. The spindle checkpoint (SC) repair pathway of noncancerous cells in exchange of flanking markers, or noncrossovers (NCOs) revealed by short patch-like repair, both of which involve gene conversion (GC) where original sequence has been replaced by the donor sequence. Abrogation of any single HR pathway that contributes to CO and NCO formation is known to result in severe genomic instability and cancer (i.e. Bloom syndrome). COs are much more deleterious than NCOs because COs can lead to loss of heterozygosity. Therefore, interventions that promote CO formation at the expense of NCOs can further sensitize cancers. My central working hypothesis is that individual HR pathways will have distinguishing temporal and qualitative features that facilitate or hinder that pathway’s ability to compensate for the loss of others. By establishing a novel system that can interrogate the kinetics of HR pathways in vivo in mammals at endogenous sites, we can determine which HR pathways are utilized in the absence of others to identify potential chemotherapeutic targets. Methods: Mouse spermatocytes were synchronized using an inhibitor WIN 18,446 followed by retinoic acid injection. Synchronized cells at early, mid-, and late prophase I were isolated by flow cytometry, and the level of synchrony was determined by immunofluorescence. Recombination analysis on synchronized cells was performed by PCR at hotspots. Results: My temporal analysis shows that there are two classes of NCOs: distal NCOs away from the hotspot center that are formed during early prophase I, and central NCOs that are formed coincidentally with MLH1/3-dependent COs in the hotspot center during mid-prophase I. To analyze CO formation by structure-selective nucleases (SSNs) and distortion pathways, I examined recombination in the absence of mismatch repair or female meiotic CO resolvasome activity. Synchronized spermatocytes revealed a reduction in COs and concomitant increase in long NCOs consistent with dissolution by RecQ helicases. In these mice, dissolution and SSNs do not become apparent until late prophase I. Conclusions: By utilizing the system I have established, I will test the impact of small-molecule inhibitors of RecQ helicases by direct in vivo injection.
whole exome sequencing of 18 tumors from unrelated individuals with a family history of glioma collected through the Giogene International Consortium. Methods: FFPE specimens were sequenced and reviewed to localize neoplastic tissue for DNA extraction. Sample QC, library preparation, exome plus targeted capture including the TERT promoter region (TERTp), and paired-end sequencing on the Illumina HiSeq 2000 platform were performed at the Baylor College of Medicine Human Genome Sequencing Center (HGSC). Interlaboratory QC sequence data were analyzed using the HGSC Mercury pipeline and mutations were called with respect to blood-derived germline DNA sequencing data for each case using MuTect v1.1.7. Variants were annotated using Oncotator, COSMIC, and dbSNP databases. Copy number profiling was performed using the Illumina HumanOmniExpress BeadChip and analyzed using Illumina GenomeStudio v2.0. Results: Exome sequencing was completed at an average read depth of 116X with 97% of targeted bases covered at least 10 times. We observed a median of 50.5 non-silent somatic mutations (range: 14-97) across the 18 tumors profiled. Codominance of chromosome arms 1p and 19q was observed in two cases, and TERTp hotspot mutations C228T or C250T were observed in eight. All three molecular subtypes of sporadic glioma were observed, including IDH1-mutant, 1p/19q intact (n=2), IDH1-mutant, 1p/19q intact (n=2), and IDH1-wildtype tumors (n=9). Characteristic subtype-specific mutations (e.g., TP53 and ATRX mutations among IDH1-mutant, 1p/19q intact) were observed in most cases. For two cases with previously reported germline mutations in telomere shelterin complex gene POT1, the first (POT1 E450X) displayed somatic IDH1 mutation, 1p/19q deletion and a compound heterozygous POT1 mutation (n=1) while the second (POT1 G95C) displayed a somatic IDH1 mutation without 1p/19q deletion or POT1 loss of heterozygosity. Neither case had acquired TERTp or ATRX mutations. Conclusions: This study highlights the role that deleterious germline mutations play in compromising molecular pathways required for gliomagenesis, as exemplified by the absence of typical acquired mutations in telomere regulation in cases with germline POT1 mutation. Outside of these select cases, the genomic landscape of gliomas in this study largely recapitulates that which is seen in sporadic glioma.

**CPRIT Grantee Poster Session A**

**41 Disruption of apicobasal polarity impairs endometrial development and promotes endometrial tumorigenesis**

**Erin Williams, The University of Texas System; R. Broaddus; A. Gladden**

**Introduction:** Unlike most cancer types, the incidence and mortality of endometrial cancer is increasing and onset is occurring at younger ages. This is particularly concerning in light of the importance of uncovering the basic mechanisms of endometrial tumorigenesis. Disruption of cell polarity is frequently observed in epithelial cancers, but is not well studied in endometrial cancer. The epithelium of the endometrial gland, the primary cell type thought to give rise to endometrial cancer, is shed and re-established after each menstrual cycle. This continual cell replacement requires a constant reorganization of the epithelium. We investigated the status of apicobasal polarity in low-grade endometrial cancer to assess the role of polarity in early endometrial tumor development. Methods: We utilized human tissue samples and endometrial cancer cell lines to examine the effects of apicobasal polarity on endometrial epithelial polarity. In addition, in order to understand how apicobasal polarity is working within the uterus in vivo, we generated a mouse model. We deleted Merlin (gene: NF2), an apicobasal polarity regulator, within the uterus (NF2lox/lox; Wnt7a-Cre (NF2loxK0) or NF2lox/lox; FrCre NF2K0PR). Results: We determined that Par3, an apical polarity protein, localizes to the apical region in normal human endometrial glandular epithelium, however in low-grade tumor samples Par3 was mislocalized. Additionally, we found that many endometrial cancer cell lines also show a decrease in Par3 protein levels. Reinforcement of Par3 resulted in decreased proliferation and cell death, as well as increased differentiation of markers associated with differentiation. Since Notch receptor localization was shown to be affected by Merlin, a Par3 regulator, we examined the Notch receptors in endometrial cancer cell lines and found an increase in membrane localization when Par3 was unexpressed. In addition, in human endometrial tissue samples, we determined that Notch receptors localize to the basolateral membrane in normal endometrial glands but are diffuse in low-grade cancer samples. Since Notch receptors must be localized properly to interact with the transmembrane Notch ligands, we examined downstream targets and found that the oncogenic target genes were decreased in endometrial tumors. In order to understand how polarity affected the endometrium in vivo, we examined our NF2K0 mice. Merlin-deficient endometrium displays a loss in endometrial gland formation and an aberrant stratification of the luminal epithelium. Conclusions: Apicobasal polarity is involved in both endometrial development and tumorigenesis mediated through the regulation of transmembrane receptor signaling that maintains normal proliferation and differentiation.

**42 CPRIT Grantee Poster Session B**

**42 Dependency of Radiation Dose Levels on The Treatment Responses in AT1 Prostate Tumors in Rats Tatsuya Araki, The University of Texas Southwestern Medical Center; T. Chiu; J. Campbell; D. Yang; S. Stojadinovic; R. Mason**

**Introduction:** Previous studies have shown that, in the prostate tumor (Dunning subline R3327-AT1), larger responses of blood-oxygen-level-dependent (BOLD) and tissue-oxygen-level-dependent (TOLD) MRI to radiation treatment were observed in tumors with lower initial oxygenation and growth delay following irradiation. The earlier studies employed a total amount of radiation dosage of 30 Gy. We hypothesized that the application of greater dosage would neutralize the tumor control effects of oxygen response. In this research, we tested the dose response of MRI in a preliminary study, various levels of radiation dosages were tested to investigate their tumor control effects. Methods: Radiation Treatment: Tumors were irradiated with a single dose using a small animal X-ray irradiator. The dosage levels (ranging from 30 to 80 Gy with 10 Gy increment) were selected for each tumor in a balanced order. The endpoint of this study was 200 days after irradiation without a sign of tumor regrowth. Results: The number of tumors treated with 30, 40, 50, 60, 70, and 80 Gy were 1, 3, 3, 4, and 3, respectively. One control tumor did not receive the radiation. Relatively low and high dose groups consist of tumors receiving 30–50 Gy and 70–80 Gy, respectively. Local Tumor Control: The tumor control rates (TCoS) of tumors varied for the initial oxygen levels. The results show that TCoS is dose-dependent. Conclusions: The earlier studies employed a total amount of radiation dosage of 30 Gy. We hypothesized that the application of greater dosage would neutralize the tumor control effects of oxygen response. In this study, the dose response of MRI in a preliminary study, various levels of radiation dosage were tested to investigate their tumor control effects.

**43 CPRIT Grantee Poster Session A**

**43 Telomerase Reactivation In The Lgr5+ Cells Rescues Stem Cell Depletion Through Suppressing The ER/UPR Stress Pathway Deepavali Chakravarti, The University of Texas M.D. Anderson Cancer Center; R. DePinho; B. Hu; A. Wang**

**Introduction:** Telomere shortening has been correlated with several autoimmune and pathogenic conditions such as inflammatory bowel disease and ulcerative colitis. Inflammatory bowel disease has been established as a significant risk factor for developing colon cancer. GWA studies have revealed ER stress related proteins play important role in the initiation of such inflammatory bowel diseases. Late generation (G4) of the telomerase deficient mice exhibit symptoms of inflammatory bowel disease and neoplasia of both the small and the large intestine by 6 months of age compared to the early generation counterpart (G0) and can be an excellent model to study the progression of inflammatory bowel disease to colon cancer development. Closer examination revealed an increase in ER stress protein expression in the stem cell compartment leading to premature differentiation of the stem cells to a more progenitor like population. Telomerase reactivation reverses the phenotype and extends the lifespan of these mice. Methods: In order to study the role of telomerase activation in the intestinal compartment we crossed the late generation telomerase deficient LSL-mTert animals to the tamoxifen inducible Lgr5-EGFP CreERT2 model. In this model we could reactivate telomerase at desired time specifically in the intestinal stem cell compartment. We characterized the intestines with immunohistochemical analyses and electron microscopy. With the help of beta galactosidase lineage tracing experiments and BrDU incorporation assay we determined the proliferation rate and the cell turn over rates in these animals. We performed RNAsq and qPCR analysis. We also isolated crypts and performed organoid cultures from early and late generation of the animals. Results: Unexpectedly we found that the intestinal crypts from the G4 mice showed neoplastic lesions and crypt degeneration accompanied by high degree of immune infiltrates. Young G4 animals exhibit elevated rate of apoptosis, cell turn over and proliferation in comparison to the G0 mice. RNA-seq indicated upregulation of the ER phagosophal pathway and immune pathways. Increase in ER stress was further confirmed by electron microscopic analysis, IHC and qPCR. Interestingly reactivation...
of telomerase specifically in the Lgr5+ stem cells suppressed the ER/UPR pathway and reduced stem cell proliferation and loss through differential control of the increased lifespan.

**Conclusions:** In conclusion telomerase reactivation preserves stem cell loss by reducing ER stress and thereby extends lifespan.

### 45 CPRIT Grantee Poster Session A

#### Modeling Hereditary Retinoblastomas-associated Osteosarcoma by Engineered hESCs

**Introduction:** Osteosarcoma is the most common malignancy bone tumor among children and adolescents. The five-year overall survival of localized osteosarcoma hovers around 60-70%, but dramatically decreases to 20-30% for metastatic patients. Retinoblastoma is the most frequent eye cancer in children. About 1/3 of patients with retinoblastoma harbor the germline RB1mutation, resulting in the development of retinoblastoma. The much higher incidence of osteosarcoma was found in patients with hereditary retinoblastoma than sporadic retinoblastoma. However, the underlying mechanisms are still partly understood.

**Methods:** (1) We apply CRISPR/Cas9 genome editing to generate RB1 hotspot mutations in human embryonic stem cells (hESCs) to model bone malignancy in hereditary retinoblastoma (RB) patients. (2) We define pluripotent characteristics of the RB1 mutated hESCs by both qRT-PCR and immuno-staining. (3) We examine if RB1 mutated hESCs derived osteosarcoma cells harbor the germline RB1 mutation. (4) We apply RNAseq and CHIP-seq to identify the transcriptome and genome alterations in RB-associated osteosarcoma. **Results:** Three hotspot mutations (c.1333C>T, c.1363C>T, and c.1400T>C) of RB1 are individually generated in hESC H1 line as H1(RB1mtRB1) by CRISPR/Cas9 genome editing methodology. All of these clones carrying heterozygous RB1 mutation mimics genetic pattern of RB. RB1 mutation in H1(RB1mtRB1) is further confirmed by Sanger sequencing and western blot. The H1(RB1mtRB1) lines express pluripotency factors (NANOG, OCT4 and SOX2), hESC surface markers (TRA-1-81 and SSEA4) as well as microtubule targeting agents by targeting CHEK1 Xiaojia Yu; The University of Texas Southwestern Medical Center; H. Zhu; X. Wang

**Introduction:** Targeting neuroblastoma stem cells using CRISPR/Cas9 Julie Tomolinos, Baylor College of Medicine; S. Agarwal; J. Shohet

**Conclusions:** The proposed method successfully imposes the orthogonality between the distinctive structures of two datasets to avoid additional common structure being retained therein.

**Conclusion:**

**46**

**ABSTRACTS**

**Poster Session B**

**Targeting neuroblastoma cancer stem cells using CRISPR/Cas9**

Julie Tomolinos, Baylor College of Medicine; S. Agarwal; J. Shohet

**Results:** We designed high specificity sgRNAs flanking exons 8 and 9 of the CSF3R gene. This is a highly-conserved cytokine receptor domain that allows for G-CSF receptor activation and dimerization. sgRNA were synthesized using PCR amplification and in vitro transcription. Ribonucleoprotein (RNP) complexes of Cas9 protein and sgRNA were electroporated into NB cell lines (SH-SY5Y & NGP) and a control cell line (BeWo). Potential mutant clones were characterized using qRT-PCR for mRNA, Western blot for protein expression, and flow cytometry for CD114 surface expression.

**Conclusions:** We designed several sets of sgRNA guide pairs and electroporated the Cas9 RNP mix into BeWo cells, a placent cell line, which can be used for drug sensitivity testing. We found that cytokine G-CSF treatment increases NB tumor growth and metastasis with an increase in total CD114+ cells in vivo. Here, we utilized the advanced CRISPR/Cas9 mediated genome editing tool to directly target NB CSC subpopulation. This study will provide better understanding of the role of CD114 in NB tumorigenicity and in CSC maintenance. **Methods:** We designed high specificity sgRNAs flanking exons 8 and 9 of the CSF3R gene. This is a highly-conserved cytokine receptor domain that allows for G-CSF receptor activation and dimerization. sgRNA were synthesized using PCR amplification and in vitro transcription. Ribonucleoprotein (RNP) complexes of Cas9 protein and sgRNA were electroporated into NB cell lines (SH-SY5Y & NGP) and a control cell line (BeWo). Potential mutant clones were characterized using qRT-PCR for mRNA, Western blot for protein expression, and flow cytometry for CD114 surface expression. **Results:** We designed several sets of sgRNA guide pairs and electroporated the Cas9 RNP mix into BeWo cells, a placental choriocarcinoma cell line with high expression of CD114. Depending on the sgRNA guide pair, we achieved 100% knockout efficiency as determined with PCR genotyping. Furthermore, the genomic knockout efficiency is found to be correlated with reduction in CD114 surface expression as determined with flow cytometry. NB cell lines were electroporated using optimized constructs with about 40% editing efficiency. Promising NB CD114 knockout clones have been isolated and further studies to determine the effects of CD114 knockout on NB growth, drug response, and tumorigenicity are ongoing. **Conclusions:** NB cell lines can be efficiently edited by CRISPR/Cas9 based genomic editing method. CSF3R exons 8 and 9 are essential for CD114 function and knockout of these exons leads to the loss of CD114 surface expression.

**47**

**ABSTRACTS**

**Poster Session B**

**Extracting common and distinctive structures from genomic datasets**

Hai Shu, The University of Texas M.D. Anderson Cancer Center; H. Zhu; X. Wang

**Results:** It often occurs in medical sciences that multiple types of data are measured on a common set of objects. For example, The Cancer Genome Atlas (TCGA) collected genomic data on various platforms for human cancer tumors. A typical model for jointly analyzing two such datasets is to decompose each dataset into a common structure containing the shared information between datasets, a distinctive structure characterizing the individual information within each single dataset, and residual noise. Existing methods often focus on the orthogonality between the common and distinctive structures, which distracts their attention from the more important orthogonality between the two distinctive structures. **Methods:** We introduce a novel decomposition method based on the canonical variables that are sequentially obtained closest features between two datasets. We carefully define the common and distinctive components for these canonical variables, and then collect them to form the desirable common and distinctive structures of two datasets. **Results:** The proposed method outperforms state-of-the-art methods in both simulated data and the TCGA datasets of human breast cancer. **Conclusions:** The proposed method successfully imposes the orthogonality between the distinctive structures of two datasets to avoid additional common structure being retained therein.

### 48 CPRIT Grantee Poster Session B

#### miR-195 regulates the response of non-small cell lung cancer to microtubule targeting agents by targeting CHEK1 Xiaojia Yu; The University of Texas Southwestern Medical Center; H. Zhu; X. Wang

**Introduction:** microRNAs (miRNAs) are a family of small non-coding RNAs (18-24 nt) that post-transcriptionally repress gene expression by direct binding to the 3’ untranslated regions (UTRs) of their targets. By targeting cancer-related genes, miRNAs have been shown not only to...
regulate cancer growth/progression, but also to modulate the response of cancer cells to chemotherapy. Such miRNAs are potential candidates for therapeutic intervention. **Methods:** Aiming to identify functional miRNAs in non-small cell lung cancer (NSCLC), we performed a high-throughput screen and found that miR-195 inhibits the growth of NSCLC cells and sensitizes them to microtubule-targeting agents (MTAs), a family of chemotherapeutic drugs widely used for NSCLC treatment. The function and mechanism of miR-195 in NSCLC cells are now the focus of our research. **Results:** We demonstrated that miR-195 synergizes with both an old-school MTA (paclitaxel) and a new-fangled one (eribulin) to repress the growth of NSCLC cells. Over-expression of miR-195 sensitizes NSCLC cells to paclitaxel and eribulin, while knock-out of miR-195 confers resistance to paclitaxel and eribulin. Importantly, lung tumor growth of miR-195 over-expression are more sensitive to eribulin treatment than control tumors. Induced expression of miR-195 in lung tumors potentiates the efficacy of eribulin to repress tumor growth. Additionally, we showed that miR-195 directly targets CHEK1 to regulate the response of NSCLC cells to paclitaxel and eribulin. The direct and specific binding of miR-195 to the 3′UTR of CHEK1 was confirmed by luciferase reporter assay. Repression of CHEK1 contributes to the resistance to paclitaxel and eribulin in NSCLC cells. Analysis of TCGA data show that CHEK1 is significantly up-regulated in lung tumors compared to adjacent normal tissues and that its up-regulation is associated with worse recurrence-free and overall survival. **Conclusions:** We report the identification of miR-195 as a sensitizer to microtubule-targeting agents in NSCLC, mediated by its repression of CHEK1. Mouse xenographs with induced or constitutive over-expression of miR-195 show that tumors with high miR-195 expression are more sensitive to drug treatment and that induction of miR-195 potentiates the efficacy of eribulin in repressing tumor growth. These results highlight the potential application of miR-195 expression as a biomarker to predict patient response to MTAs and the potential for delivery of miR-195 mimics as an adjuvant to chemotherapy.

**51**

**CPRIT Grantee Poster Session A**

**Biodegradable multilayered nanofilms for cancer cell isolation and recovery**

**Wei Li; Texas Tech University; Z. Dong**

**Introduction:** Selective isolation and purification of circulating tumor cells (CTCs) from whole blood is an important capability for both clinical medicine and biological research. Current techniques to perform this task place the isolated cells under excessive stresses that reduce cell viability. Biodegradable films are expected to partially induce phenotype change, therefore losing valuable information about the isolated cells. The goal of our work is to effectively isolate as well as non-inversely recover cancer cells using a microfluidic device coated with a biodegradable multilayered nanofilm. To this end, we have applied layer-by-layer (LbL) assembly to create a library of ultrathin coatings using a broad range of materials through complementary interactions. **Methods:** We systematically studied the effect of various flow conditions and channel geometries on the thickness and surface roughness of the resulting films. We also investigated the biocompatibility and degradation behaviors of a series of enzymatically-degradable films from naturally derived polymers, e.g., a LbL nano-film coating with an affinity-based cell-capture surface that is capable of selectively isolating cancer cells from whole blood, and that can be rapidly degraded on command, we are able to gently isolate cancer cells and recover them without compromising cell viability or proliferative potential. **Results:** This film system has been applied to two capture and release platforms: 1) microfluidic HB chip and 2) hollow microtubule-targeting agents in NSCLC, mediated by its repression of CHEK1. Mouse xenographs with induced or constitutive over-expression of miR-195 show that tumors with high miR-195 expression are more sensitive to drug treatment and that induction of miR-195 potentiates the efficacy of eribulin in repressing tumor growth. These results highlight the potential application of miR-195 expression as a biomarker to predict patient response to MTAs and the potential for delivery of miR-195 mimics as an adjuvant to chemotherapy.

**52**

**CPRIT Grantee Poster Session B**

**ClinP: Fast subclonal architecture reconstruction from whole-genome sequencing data**

**Kaixian Yu; The University of Texas M.D. Anderson Cancer Center; M. McGrail; T. Liao; N. Sahni**

**Introduction:** Tumors as well as various human tissues usually consist of different subpopulations (subclones) that are characterized by somatic mutations. The composition of such subpopulations may affect disease progression and treatment efficacy. And understanding the subclonal structure helps infer the evolutionary history of cells which can further guide the discovery of driver mutations such as those in cancer studies. Currently most subclonal reconstruction methods are Dirichlet Process (DP) based, requiring expensive computing since MCMC algorithm is commonly adopted to solve the problem, and careful post-processing data is required. We develop a model named Copy Number Inference and Prediction (ClinP) that jointly infers content and copy numbers of single nucleotide variations (SNVs) in the DP setting. **Methods:** We present ClinP (Clonal structure identification through penalizing pairwise difference), a fast and minimum post-processing algorithm for calling subclonal structures using whole-genome sequencing data. ClinP deterministically solves a penalized likelihood problem, making execution much faster. **Results:** In a simulated sample with 15,000 SNVs, it takes ClinP less than 1 hour to finish the subclonal reconstruction, which is about 100 times faster than other methods. ClinP is also capable of handling sequencing data at low coverages (30X-60X). Based on 125 simulated samples, ClinP showed comparable prediction performance with DP-based methods. In the application to ICGC whole-genome sequencing data from 2,703 tumor samples from 39 cancer types, ClinP provided results within 4 days and was able to analyze the hypermutator (>100,000 SNVs) samples correctly. **Conclusions:** We have proposed ClinP, a fast and accurate subclonal reconstruction method that requires minimum post-processing. It is especially suitable for quickly processing large cohorts containing thousands of whole-genome sequencing data to analyze cancer heterogeneity and their evolutionary histories.
**Introduction:** Epithelial-mesenchymal transition (EMT) occurs during embryonic development, wound healing, carcinogenesis and certain other circumstances. Since the migration and invasion capabilities of cancer cells usually associates with their metastatic potential, EMT has been considered crucial for cancer metastasis. Twist1 is a basic helix-loop-helix domain-containing transcription factor (TF) expressed in multiple types of cancer cells. In breast cancer cells, Twist1 expression induces EMT, stemness-like properties, invasion and metastasis in vivo. However, the specific role of Twist1 has not been well defined during the entire process of a spontaneous breast tumor initiation, progression and metastasis in vivo.

**Methods:** We developed two genetic mouse models of breast cancer in which Twist1 is either wild type (WT) or specifically deleted in the oncogene-expressing cells (CSCs). Using immunohistochemical and chemical analysis, we examined the expression patterns of epithelial/mesenchymal markers and EMT inducing TFs, as well as quantitatively analyzing circulating tumor cells (CTCs) and lung metastasis in these two mouse models.

**Results:** Twist1 KO showed no effects on tumor initiation and growth. In both group early tumor cells, Twist1 and mesenchymal markers were not expressed in Twist1−/− and lung metastasis was absent. Twist1 expression was detected in ~6% of the advanced WT tumor cells. Most of these Twist1+ cells co-expressed several other EMT-inducing TFs (Snail, Slug, Zeb2), lost ERα and luminal marker K8, acquired basal cell markers (K5, p63) and exhibited a partial EMT phenotype (E-cadherin+/vimentin−). In advanced tumor cells, Twist1 KO largely diminished the expression of the aforementioned EMT-inducing TFs and basal and mesenchymal markers but maintained the expression of the luminal markers. CTCs were detected in mice with advanced WT tumors but not in Twist1−/− tumors. Nearly all WT CTCs co-expressed Twist1 with ERα but ERα− alone expressing TFs and both mesenchymal and luminal markers. Mice with advanced WT tumors developed extensive lung. Mice with advanced Twist1−/− tumors developed very little lung metastasis. Therefore, Twist1 is required for the expression of other EMT inducing TFs in a small subset of tumor cells. Together, they induce partial EMT, basal-like tumor phenotype.

**Conclusion:** This study showed that Twist1 expression is commonly associated with the expression of other EMT inducing TFs in a small number of primary breast tumor cells and CTCs, programming a partial EMT and a basal-like tumor cell phenotype to drive these cells disseminate into the circulation and metastasize to the lung. Twist1 may be a potential target for controlling breast cancer metastasis.

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**Introduction:** Nuclear Receptor NR4A1 is a Tumor Suppressor Down-regulated in Triple-negative Breast Cancer Jiaxin Xu, Baylor College of Medicine; H. Wu; J. Bi; Y. Peng; L. Hua; X. Yu; Y. Zhou; L. Qin; Y. Xie

**Introduction:** The nuclear receptor (NR) superfamily contains hormone-inducible transcription factors that regulate many physiological and pathological processes through regulating gene expression. NR4A1 is an NR family member, but still does not have an identified ligand, and its role in cancer is also currently unclear and controversial. In this study, we aimed to define the expression profiles and specific role of NR4A1 in the highly malignant triple-negative breast cancer (TNBC), which still lacks available targeted therapies.

**Methods:** Age-matched normal mammary glands and mammary tumors were collected from female wild type and K14-cre; p53loxP/loxP; Brca1loxP/loxP mice, respectively. Parallel sections prepared from 60 human non-cancer breast tissues and 148 TNBC were provided by University of Texas (UT) Southwestern Medical Center, UT MD Anderson Cancer Center and Sun Yat-Sen University. Immunohistochemistry was performed to determine the expression levels of NR4A1 in both mouse and human breast tissues and tumors. Patients’ TNBC relapse-free survival was calculated using the Kaplan-Meier method and compared using the Gehan-Breslow-Wilcoxon test. Cell lines with either NR4A1 overexpression or knockdown were generated to assess the role of NR4A1 in TNBC cells. Immunoblotting, cell proliferation, cell migration, cell invasion, qPCR and xenograft mouse tumor models were performed by following commonly used protocols.

**Results:** Bioinformatic analysis revealed a decrease of NR4A1 mRNA expression in human TNBC samples. Semi-quantitative analysis of NR4A1 protein expression by immunohistochemistry also identified a progressive NR4A1 reduction during the development of mouse basal-like mammary tumors and a significant NR4A1 downregulation in human TNBC samples. Furthermore, the expression levels of NR4A1 in human TNBC were strongly associated with lymph node metastasis and disease recurrence. Moreover, ectopic expression of NR4A1 in MDA-MB-231, a TNBC cell line with little endogenous NR4A1, inhibited the proliferation, viability, migration and invasion of these cells, and these inhibitions were associated with an attenuated JNK1–AP-1–cycD1 pathway. NR4A1 expression also largely suppressed the growth, metastasis of these cell-derived tumors in mice. **Conclusions:** These results demonstrate that NR4A1 is downregulated in TNBC and restoration of NR4A1 expression inhibits TNBC growth and metastasis, suggesting that NR4A1 is a tumor suppressor in TNBC.

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**Introduction:** High-grade ovarian cancer (HGOC) shows excellent responses to standard-of-care surgery and paclitaxel/carboplatin therapy only to relapse 6-24 months later with typically resistant disease. While the origin of this recurrent, resistant disease is unclear, most believe it is acquired by the action of chemotherapeutics. Using novel stem cell technology that enables the cloning of cancer stem cells (CSCs) from epithelial cancers, we have generated large libraries of CSCs from multiple cancer types. And while these CSC clones are typically killed by standard-of-care chemotherapeutic drugs, a minor fraction shows profound resistance not only to paclitaxel/carboplatin but to a wide range of structurally unrelated chemotherapeutic drugs to which these cells had no prior exposure. We describe screens for drugs that selectively target this CSC population. As an example, libraries of 10-100,000 CSC clones were generated from individual, therapy naive, HGOC resections using technology we developed for cloning so-called “adult” stem cells from normal columnar epithelia (Wang et al., 2015). Results: Paclitaxel/carboplatin resistant CSCs were identified in CSC libraries derived from therapy naive tumors at ratios of 1:50 to 1:300. By copy number variation, these resistant variant clones proved distinct from the bulk of CSCs, and by gene expression analysis varied from sensitive clones by more than 700 differentially expressed genes. Independent resistant clones from the same library clustered with other resistant clones by both copy number variation and gene expression profiles, suggesting the possibility that resistance within a single tumor is dominated by a single type of resistant CSCs. Clones resistant to paclitaxel/carboplatin were screened in a 384-well format against a wide range of experimental drug-like molecules. These pre-existing resistant clones also proved to be profoundly resistant to a large number of structurally unrelated chemotherapeutic drugs. This same screening program identified drugs that act alone or in combination with paclitaxel to eliminate these resistant clones, suggesting a route to personalized medicine for addressing the problem of recurrent disease in HGOC. **Conclusions:** Tumors from patients with HGOC possess clonogenic CSCs including variants that are resistant to a broad spectrum of chemotherapeutics to which they have not been exposed. It is likely that such CSCs would survive standard-of-care chemotherapy and contribute to the recurrent disease seen in HGOC. We have identified known and experimental drugs that specifically eliminate these resistant variants and the overall platform represents a potential strategy to addressing the problem of recurrent disease in these patients.
**Introduction:** Small cell lung cancer (SCLC) is an aggressive neuroendocrine cancer that accounts for approximately 16% of new lung cancer diagnoses. Though SCLC is initially responsive to chemotherapy, resistance quickly develops, with 5-year survival rates below 15%. The development of novel therapies to overcome these drug resistance mechanisms has been a primary focus for the past 30 years. A study of ASCL1 in SCLC presents a potential targeted therapy for this treatment resistant cancer.

**Results:** In SCLC cells, phosphorylation of ASCL1_S155 was not found by absent reporter activity, whereas unphosphorylatable mutants retain mutation of S152 results in a transcriptionally inactive protein, as measured and in vivo. These experiments have the potential to identify a novel, mechanism-based therapy for this treatment resistant cancer.

**Conclusions:** Our findings suggest that strategies to induce ASCL1_S155 phosphorylation may represent a way to inactivate this transcription factor in SCLC, disrupting the growth of SCLC-dependent SCLC cells. Further work will include assessing the effect of phosphorylation on this oncogenic driver in the context of SCLC.

**Methods:** We generated a series of rat ASCL1_S152 mutants and assessed their transcriptional activity using an ASCL1-responsive luciferase reporter assay. To characterize the phosphorylation state of ASCL1_S155 in SCLC, we used mass spectrometry to determine phosphorylated ASCL1_S155 in H889 SCLC and human SCLC cell lines. These experiments helped to identify a novel, mechanism-based therapy for this treatment resistant cancer.

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**Investigation of DIS3L2 functions in Perlsman syndrome and Wilms tumor**

**Introduction:** Wilms tumor is the most common kidney cancer in children, yet its etiology is incompletely understood. Several recent studies have uncovered a role for loss of let-7 in its pathogenesis. One crucial mechanism through which let-7 expression is controlled is via the activity of the RNA-binding protein LIN28, which binds the precursor of let-7, and triggers the addition of a series of uridines to the 3′ end. This oligouridylated pre-let-7 is then degraded by the exoribonuclease DIS3L2.

**Methods:** We investigated the regulation of let-7 by DIS3L2 in Wilms tumor cells and in parallel in normal tissue. We isolated embryonic kidney progenitor cells thought to represent a cell of origin for Wilms tumor. In both these progenitor cells and the DIS3L2 knockout cell lines we performed let-7 qRT-PCR.

**Results:** Germline Dis3l2 knockout recapitulated some aspects of Perlsman syndrome, including renal overgrowth and genitourinary abnormalities, yet neither overgrowth nor renal tumors were observed. Contrary to the prevailing model, loss of DIS3L2 had no effect on mature let-7 expression in the cell lines nor in embryonic kidney primary cultures.

**Conclusions:** DIS3L2 is important for proper development and survival beyond birth. Although it is not a tumor suppressor gene, its role in the regulation of let-7 and as a component of the LIN28/let-7 pathway may provide insights into the role of let-7 in renal cell carcinoma.

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**Investigations on the interactions of Mre11, Sae2/CtIP, Wss1/Spartan and the proteasome in a novel pathway to repair Topoisomerase 1-DNA conjugates**

**Introduction:** Topoisomerase 1 (Top1) is an enzyme that releases topological stress during DNA metabolism by cutting DNA strands via forming a Top1-DNA conjugate, followed by re-ligation of the DNA. If the re-ligation step is inhibited by topoisomerase poisons like camptothecin (CPT), the Top1-DNA conjugate becomes irreversibly and leads to lethal DNA breaks, especially in replicating cells. Topoisomerase poisons are widely used as chemotherapeutics to selectively target cancers. A better understanding of the repair of DNA breaks with Top1-DNA conjugates can help to identify more specific targets for chemotherapy and to reduce the frequency of chemotherapeutic resistance. The classical pathway to remove Top1-DNA conjugates requires an enzyme called Tdp1. Tdp1 cleaves the linkage between Top1 and DNA after proteasome-dependent degradation of Top1. Despite its clear role in the re-ligation of Top1 gene in human patients do not cause a predisposition to cancer; this suggests alternative pathways exist to repair Top1-DNA conjugates.

**Methods:** To investigate the specific roles of the aforementioned genes in the repair of Top1-DNA conjugates we used TALENs to knockout DIS3L2 in a panel of cell lines with various levels of LIN28 expression. Additionally, to examine the role of DIS3L2 in let-7 regulation within the context of kidney development and to investigate its involvement in Wilms tumor pathogenesis, we used CRISPR-Cas9 to generate Dis3l2-mutant mice. From these mice we isolated embryonic kidney progenitor cells thought to represent a cell of origin for Wilms tumor. In both these progenitor cells and the DIS3L2 knockout cell lines we performed let-7 qRT-PCR.

**Results:** Germline Dis3l2 knockout recapitulated some aspects of Perlsman syndrome, including renal overgrowth and genitourinary abnormalities, yet neither overgrowth nor renal tumors were observed. Contrary to the prevailing model, loss of DIS3L2 had no effect on mature let-7 expression in the cell lines nor in embryonic kidney primary cultures.

**Conclusions:** DIS3L2 is important for proper development and survival beyond birth. Although it is not a tumor suppressor gene, its role in the regulation of let-7 and as a component of the LIN28/let-7 pathway may provide insights into the role of let-7 in renal cell carcinoma.

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**High-throughput sequencing of paired T cell receptor alpha and beta in human donors using custom made flow-focusing device**

**Introduction:** Single-cell sequencing is a powerful tool for simultaneously sequencing both TCRα and TCRβ from more than 2x10^5 individual T cells per experiment. A flow-focusing device compartmentalizes the mRNA from a single-T cell mRNA into a small lipid droplet, a RT-PCR reaction within the droplet phosphorylates the TCRα and TCRβ mRNA of single-cells. Subsequent high-throughput sequencing of TCRα and TCRβ linked cDNA produces paired TCRαβ sequences of single-cells. The whole procedure can be performed within 12 hours.

**Results:** From 106 human donors using custom made flow-focusing device, we obtained >30,000 TCRαβ sequences per T cell, with distinct sequence pairs on average. TCRαβ sequencing of single-cells were correctly paired at more than 92% precision.

**Conclusions:** Our novel approach allows for the high-throughput sequencing of paired T cells in human donors, providing valuable insights into the diversity and specificity of the human T cell repertoire.
TCRαβ sequencing technology is accurate and can find 100-fold more TCRαβ sequences than conventional technologies. This technology allows identifying tumor-reactive TCRs more quickly and accurately, and thus accelerates immunotherapy using the tumor-reactive TCRs.

Acknowledgement: This study was supported by UTHealth Innovation for Cancer Prevention Research Training Program Post-Doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP16001583), Defense Threat Reduction Agency underwater Award Number HDTRA1-12-C-0105, and Dell Medical School’s Texas Health Catalyst program. Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors.

**CPRIT Grantee Poster Session B**

The Y537S ESR1 mutation is a dominant driver of distant ER-positive breast cancer metastasis

**Introduction:** Estrogen receptor (ER) mutations occur at a high frequency in metastatic breast tumors in patients treated with hormonal therapy in the metastatic setting. We do not know if these mutations are involved in metastasis.

**Methods:** We generated ESR1 Y537S homozygous mutations using CRISPR Casp-9 technology. Treatment synergy was evaluated using CompuSyn. Athymic mice were used in tumor xenograft studies. ChiP-Seq and transcriptome analyses were performed.

**Results:** We generated CRISPR ESR1 Y537S mutation homozygous knock-in clones and lentiviral stable pools in MCF-7 cells. Transcriptome profiling revealed elevated expression of Hallmark pathways, including epithelial mesenchymal transition (EMT) and estrogen-regulated gene expression. Mutant cell growth was resistant to tamoxifen, but responsive to fulvestrant treatment. CRISPR Y537S mutant knock-in cells grown in the mammary fat-pad of athymic mice spontaneously metastasized to distant organs including lungs, liver, and skin. In the presence of estrogen, there was no difference in the frequency of distant macro metastases between parental wild-type ER and CRISPR Y537S mutant ER mice. However, in the absence of estrogen, mimicking aromatase inhibitor treatment, 80% of CRISPR Y537S mutant ER mice displayed overt distant metastasizes, but none were observed in parental wild-type ER mice (p=0.04). Interestingly, although CRISPR Y537S mutant ER tumors grown in the mammary fat-pad were unresponsive to tamoxifen treatment, tamoxifen significantly inhibited the growth of mutant tumors at the distant microenvironment (8-fold). Distant tumors retained ER expression and hormone sensitivity. Comparison of residual tamoxifen-treated metastatic tumors with tumors grown at the primary mammary fat-pad site using immunoblot analysis demonstrated significant reduction in estrogen-regulated gene expression, but no effect on the expression of biomarkers associated with EMT, suggesting a disconnect between EMT and metastasis in mutant ER+ breast tumors. These data are consistent with a recently identified as direct binding site targets in Y537S mutant cells compared with wide-type ER using ChiPSeq. A Y537S ER mutant-specific gene expression signature predicted poor disease-free survival of ER-positive patients using the METABRIC database, and lung-specific metastasis-free survival using Memorial Sloan Kettering dataset. The Y537S ER mutation is a driver of distant metastasis in ER-positive breast cancer cells. Although tamoxifen treatment was ineffective at reducing the growth of mutant cells grown at the primary site, it was effective at reducing distant metastasis. A Y537S ER mutant-specific gene expression signature predicted poor disease-free, and distant lung metastasis in ER-positive patients. Metastasis status is a potential new predictive factor for hormone therapy of metastatic breast cancer patients on maintenance hormonal therapy.

**Conclusion:** The Y537S ESR1 mutation is a dominant driver of distant ER-positive breast cancer metastasis.

**CPRIT Grantee Poster Session B**

Constitutive Activation of ATM in Neuroblastoma cell lines with the Alternative Lengthening of Telomeres (ALT) Phenotype Induces Resistance to DNA Damaging Agents

**Introduction:** Telomere maintenance is required for cancer growth. A non-telomerase mechanism, alternative lengthening of telomeres (ALT), is a hallmark of some cancers; 10-20% of high-risk neuroblastomas (NB) manifest ALT which is associated with a poor prognosis. There has been a paucity of patient-derived models of ALT cancers. Of 104 human NB cell lines and 32 xenografts in multi-panel genome wide scans identified as direct binding site targets in Y537S mutant cells compared with wide-type ER using ChiPSeq. A Y537S ER mutant-specific gene expression signature predicted poor disease-free survival of ER-positive patients using the METABRIC database, and lung-specific metastasis-free survival using Memorial Sloan Kettering dataset. The Y537S ER mutation is a driver of distant metastasis in ER-positive breast cancer cells. Although tamoxifen treatment was ineffective at reducing the growth of mutant cells grown at the primary site, it was effective at reducing distant metastasis. A Y537S ER mutant-specific gene expression signature predicted poor disease-free, and distant lung metastasis in ER-positive patients. Metastasis status is a potential new predictive factor for hormone therapy of metastatic breast cancer patients on maintenance hormonal therapy.

**Results:** The Y537S ESR1 mutation is a dominant driver of distant ER-positive breast cancer metastasis. We generated CRISPR ESR1 Y537S mutation homozygous knock-in clones and lentiviral stable pools in MCF-7 cells. Transcriptome profiling revealed elevated expression of Hallmark pathways, including epithelial mesenchymal transition (EMT) and estrogen-regulated gene expression. Mutant cell growth was resistant to tamoxifen, but responsive to fulvestrant treatment. CRISPR Y537S mutant knock-in cells grown in the mammary fat-pad of athymic mice spontaneously metastasized to distant organs including lungs, liver, and skin. In the presence of estrogen, there was no difference in the frequency of distant macro metastases between parental wild-type ER and CRISPR Y537S mutant ER mice. However, in the absence of estrogen, mimicking aromatase inhibitor treatment, 80% of CRISPR Y537S mutant ER mice displayed overt distant metastasizes, but none were observed in parental wild-type ER mice (p=0.04). Interestingly, although CRISPR Y537S mutant ER tumors grown in the mammary fat-pad were unresponsive to tamoxifen treatment, tamoxifen significantly inhibited the growth of mutant tumors at the distant microenvironment (8-fold). Distant tumors retained ER expression and hormone sensitivity. Comparison of residual tamoxifen-treated metastatic tumors with tumors grown at the primary mammary fat-pad site using immunoblot analysis demonstrated significant reduction in estrogen-regulated gene expression, but no effect on the expression of biomarkers associated with EMT, suggesting a disconnect between EMT and metastasis in mutant ER breast tumors. These data are consistent with a recently identified as direct binding site targets in Y537S mutant cells compared with wide-type ER using ChiPSeq. A Y537S ER mutant-specific gene expression signature predicted poor disease-free survival of ER-positive patients using the METABRIC database, and lung-specific metastasis-free survival using Memorial Sloan Kettering dataset. The Y537S ER mutation is a driver of distant metastasis in ER-positive breast cancer cells. Although tamoxifen treatment was ineffective at reducing the growth of mutant cells grown at the primary site, it was effective at reducing distant metastasis. A Y537S ER mutant-specific gene expression signature predicted poor disease-free, and distant lung metastasis in ER-positive patients. Metastasis status is a potential new predictive factor for hormone therapy of metastatic breast cancer patients on maintenance hormonal therapy.

**Conclusion:** The Y537S ESR1 mutation is a dominant driver of distant ER-positive breast cancer metastasis.

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**CPRIT Grantee Poster Session A**

Intra-tumor heterogeneity analysis of immune response in early stage of non-small cell lung carcinoma using multiplex immunofluorescence and image analysis approaches:

**Methodology and preliminary results**

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- P. Futreal
- J. Zhang
- I. Wistuba

**Introduction:** Tumors are composed by subpopulations of cells with distinct genetic, epigenetic and phenotypic features known as intra-tumor heterogeneity (ITH). The development and progression of non-small cell lung carcinomas (NSCLCs) is associated with the interaction between carcinoma cells (CCs), carcinoma stromal (CS) cells and tumor-associated immune-cells (TAICs) such as T-cell lymphocytes (TCLs) and tumor-associated macrophages (TAMs). The aim of this study was to characterize the ITH and immune contexture of NSCLC at early stages using image analysis and multiplex immunofluorescence (mIF) approaches.

**Methods:** Forty-eight formalin-fixed, paraffin-embedded FFPE lung-tumor tissues from resected NSCLCs were obtained. Two panels for immune profiling were validated, panel 1: AE1/AE3 pan-cytokeratin, PD-L1, PD-1, CD3, CD8, and CD68; panel 2: AE1/AE3, CD3, CD6, Granzyme-B (GB), CD45RO, and FOXP3. Three not adjacent, intra-tumor heterogeneity analysis of immune response in early stage of non-small cell lung carcinoma using multiplex immunofluorescence. A Y537S ER mutant-specific gene expression signature predicted poor disease-free survival in a Memorial Sloan Kettering dataset.

**Conclusions:** Preliminary multi-regional analysis of early stages NSCLC showed that the most important intra-tumor phenotypes of TCLs detected are co-inhibited or inactive phenotypes. The phenotypic ITH of TCLs observed in NSCLC can be used as a signature that differentiates from the SCC histology. Ongoing studies of a larger cohort of cases and correlation with clinical and pathological characteristics, including patients’ outcome are warranted.

**References:**

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Mechanisms of resistance towards a rational combined tyrosine kinase inhibitor therapy in triple-negative breast cancer (TNBC). Ching-Chung, Baylor College of Medicine; T. Sun; A. Nair; S. Kuriel; N. Neill; S. Tyagi; M. Orellana; R. Dominguez-Vidana; D. Chan; K. Sheng; L. Dobrolecki; R. Mao; C. Nagi; T. Wang; R. Schift; C. Gutierrez; M. Elosegui; G. Hilsenbeck; C. Shaw; C. Zong; A. Malovanay; B. Zhang; M. Ellis; C. Cobuzio; S. Kim; T. M. Lewis; T. G. Shaw; C. Wang.

**Introduction:** Triple-negative breast cancer (TNBC) is a common subtype of breast cancer that confers a poor prognosis; median survival for metastatic TNBC patients is only 13 months. Currently, there is no effective therapeutic targeted strategies available for TNBC due to our lack of understanding of the molecular drivers of the disease. Using a targeted genetic screen, we recently identified the tyrosine phosphatase PTPN12 as a novel tumor suppressor that is frequently compromised in TNBC (Sun, Cell 2012). Mechanistically, PTPN12 serves as a feedback inhibitor of the molecular target of the drug resistance to this combination TKi therapy that support resistance in these TNBC models. Conclusions: We are currently exploring if these pathways can be utilized to enhance efficacy of our rational combined TKi therapy in TNBC patients.

**SNV impact prediction in a pathway-based framework**

**Poster Session A**

**Cancer Biology**

**CPRIT Grantee Poster Session A**

**63**

**Identification of infrequently mutated cancer driver genes through SNV impact prediction in a pathway-based framework**

**Amandha Kaur, Baylor College of Medicine; T. Hsu; P. Katsonis; C. Pickering; J. Myers; M. Frederick; O. Lichtarge**

**Introduction:** Attempts to identify driver genes of cancer and other complex diseases have traditionally focused on high mutation frequency as a signal of positive selection. As a result, limited statistical power and the loss of the “long tail” of infrequently mutated genes understudied, as well as many of the pathways they belong to. Using Pathway-EA, we address both problems jointly by detecting pathways that contain groups of genes under collective mutational positive selection. We hypothesize that if multiple genes are capable of disrupting a function when mutated, functionally related, and targeted to be mutated at a low frequency individually but a high frequency overall. Consequently, rare driver genes may operate in pathways together and be collectively biased toward impactful mutations, indicating positive selection. This approach is novel in that it represents integration of the EA equation over pathways and is a fundamentally new representation of evolutionary processes via the language of calculus. Methods: For 12 cancer types, somatic missense mutations were obtained through TCGA and annotated with AnnoVAR and Evolutionary Action (EA). Significant (q-value < 0.1) single gene results were identified by comparing the distribution of each gene’s EA impact scores to the EA profile of the cancer as a whole and were excluded from further analysis. In order to identify additional cancer drivers for each cancer, the remaining genes were considered on the pathway level using pathways curated by the Reactome database. Each pathway was optimized by leave-one-out analysis to identify the subset of genes in the pathway that mediated bias toward high action mutations. Optimized gene subsets significant after FDR correction and also more significant than at least 95% of the modules obtained from randomly simulated pathways of the same size were considered to contain candidate drivers. Results: Computational validation revealed that our candidates were enriched for cancer-related genes, showed independent markers of positive selection in cancer, and were under negative selection in healthy germline exomes. In addition, we experimentally tested 78 of the top novel predictions for head and neck cancer (HNSC) using shRNA screens performed on both HPV+ and HPV- cell lines. In both cell lines, predicted drivers had rankings consistent with their role as drivers and were significantly overrepresented amongst hits from the screen. Conclusions: Pathway-EA can identify positive selection acting on groups of genes and can discover novel drivers of phenotype.

**64**

**SRC-2-mediated Coactivation of Anti-tumorigenic Target Genes Suppresses MYC-induced Liver Cancer**

**Shruthi Suresh, The University of Texas Southwestern Medical Center; D. Durakoglugil; X. Zhou; B. Zhu; S. Comerford; C. Xing; X. Xie; B. York; K. O’Donnell**

**Introduction:** Hepatocellular carcinoma (HCC) is the fifth most common solid tumor in the world and the third leading cause of cancer-associated deaths. A transposon mutagenesis screen previously performed in our lab identified mutual binding of SRC-2 and the coactivator p53 to accelerate liver tumorigenesis. This revealed a tumor suppressor role for Steroid Receptor Coactivator 2/Nuclear Receptor Coactivator 2 (Src-2/Ncoa2) in liver cancer. In contrast, SRC-2 was recently shown to promote survival and metastasis in prostate cancer cells, suggesting a tissue-specific role for SRC-2 in tumorigenesis. Methods: To definitively test the tumor suppressor activity of SRC-2 in MYC-induced liver cancer in vivo and to further investigate the mechanism(s) through which this coactivator inhibits liver tumorigenesis, we examined the consequences of genetic deletion of Src-2 in a MYC-induced liver cancer model. RNA sequencing, in vivo chromatin immunoprecipitation (ChIP), and functional experiments were performed to identify direct targets that contribute to SRC-2-mediated tumor suppression. Results: Src-2–/– mice exhibited a significant enhancement of liver tumor burden compared to Src-2+/+ animals. RNA sequencing of liver tumors and in vivo ChIP assays further revealed a set of direct target genes that are bound by SRC-2 and exhibit downregulated expression in Src-2–/– liver tumors. Inhibition of SRC-2 or select SRC-2 target genes including SHP (Small Heterodimer Partner), DKK4 (Dickkopf-4), and CADM4 (Cell Adhesion Molecule 4) accelerated proliferation of human liver cancer cells in vitro and tumorigenesis in vivo, while overexpression of SRC-2 targets, or SRC-2 itself, resulted in tumor suppressive effects. Conclusions: Our study demonstrates that genetic inactivation of Src-2 is sufficient to accelerate MYC-mediated liver tumorigenesis. These data also suggest that SRC-2 may exhibit an oncosuppressor activity depending on the target genes and nuclear receptors that are expressed in distinct tissues and illuminate the mechanisms of tumor suppression by SRC-2 in liver. Moreover, our findings illustrate how combining unbiased forward genetic approaches with cancer genomics and mouse modeling enables functional annotation of genes in human malignancies.
Harnessing mitochondrial dysfunction as target for cancer therapy
Natasha Kirienko, Rice University

Introduction: Under normal conditions, mitochondria undergo constant fusion and fission events that facilitate turnover of damaged material via autophagic degradation (commonly called mitophagy). This process is disrupted in many cancers, leading to an intrinsically fragile-low-level mitochondrial activity decreases ROS and provides raw material for cell division, which can mediate its expression and activation. Studies employing whole animal models and loss of tumour suppressor capacity, leading to the formation of colon tumors. Furthermore, regulation of gastrointestinal function and toxicant exposure. Hits and the genetic profile will be validated in cancer cell lines.

Results: Using a high-throughput assay, we screened ~50,000 compounds for novel small molecules that efficiently activate mitophagy. The screen yielded approximately 150 primary hits. Many belonged to structurally-related clusters. Initial characterization and prioritization of hits is underway. Using C. elegans, we looked for genetic markers indicative of increased sensitivity to mitophagic activators. We assembled a set of ~300 C. elegans genes orthologous to known pro-oncogenes and tumor suppressors (e.g., lin-35/Retinoblastoma, cep-1/p53, cul-1/Cullin1, etc.) and genes frequently mutated in cancers (e.g., dpy-6/MUC16/MUC4, unc-68/RYR2, F42H10.3/NEB, etc.). A subset of these genes, when mutated, caused precocious mitophagic activation and increased sensitivity to multiple autophagic chemotherapeutics. Importantly, RNAi knockdown of most of these genes did not adversely impact lifespan in the absence of drugs. These genes were used as a seeding set to build and expand a network that provides a mutational signature predicting sensitivity to mitotoxic drugs. Conclusions: We are using a multifaceted approach to develop a new kind of cancer treatment. We are building a genetic signature that predicts the sensitivity of patients' cancers to mitophagic activators. We are also optimizing novel mitophagy-inducing chemotherapeutics. Treatments and the genetic signature will be validated and optimized in a panel of cancer cell lines.

Targeted deletion of the Aryl Hydrocarbon Receptor in the colonic epithelium promotes the development of aberrant crypt foci in mice fed a high fat diet.
Erika Garcia-Villatoro, Texas A&M University; L. Davidson; C. Allred; M. Hensel; R. Menon; A Jayaraman; S. Safe; R. Chapkin; C. Allred

Introduction: Colorectal cancer is the third leading cause of cancer mortality in the United States. As indicated by a growing body of epidemiological data, obesity and consumption of a high fat diet (HFD) have been strongly associated with an increased risk of colon cancer, as well as an increase in the number and function of intestinal stem cells and loss of tumor suppressor capacity, leading to the formation of colon tumors. Furthermore, regulation of gastrointestinal function and toxicant metabolism is mediated by the aryl hydrocarbon receptor (AhR). AhR is a ligand-activated transcription factor widely expressed in the intestinal epithelium where components of the diet and microbial metabolites can mediate its expression and activation. Studies employing whole animal knockout of AhR have reported an enhanced onset of sporadic colorectal tumors. In parallel, a bioinformatic approach was used to generate a network of genes whose mutation confers sensitivity to mitophagic activation. Hits and the genetic profile will be validated in cancer cell lines. Results: Using a high-throughput assay, we screened ~50,000 compounds for novel small molecules that efficiently activate mitophagy. The screen yielded approximately 150 primary hits. Many belonged to structurally-related clusters. Initial characterization and prioritization of hits is underway. Using C. elegans, we looked for genetic markers indicative of increased sensitivity to mitophagic activators. We assembled a set of ~300 C. elegans genes orthologous to known pro-oncogenes and tumor suppressors (e.g., lin-35/Retinoblastoma, cep-1/p53, cul-1/Cullin1, etc.) and genes frequently mutated in cancers (e.g., dpy-6/MUC16/MUC4, unc-68/RYR2, F42H10.3/NEB, etc.). A subset of these genes, when mutated, caused precocious mitophagic activation and increased sensitivity to multiple autophagic chemotherapeutics. Importantly, RNAi knockdown of most of these genes did not adversely impact lifespan in the absence of drugs. These genes were used as a seeding set to build and expand a network that provides a mutational signature predicting sensitivity to mitotoxic drugs. Conclusions: We are using a multifaceted approach to develop a new kind of cancer treatment. We are building a genetic signature that predicts the sensitivity of patients' cancers to mitophagic activators. We are also optimizing novel mitophagy-inducing chemotherapeutics. Treatments and the genetic signature will be validated and optimized in a panel of cancer cell lines.

PepQuery enables fast, accurate, and convenient cancer proteogenomic analysis
Bo Wen, Baylor College of Medicine; X. Wang; B. Zhang

Introduction: Cancer genomics studies have identified a large number of genomic alterations that may lead to novel, cancer-specific protein sequences. Proteins resulted from these genomic alterations are attractive candidates for cancer biomarkers and therapeutic targets. The leading approach to proteomic validation of genomic alterations is to analyze tandem mass spectrometry (MS/MS) data using customized proteomics databases created from genomics data. Such analysis is time-consuming and requires thorough training and detailed knowledge in proteomics data analysis, leading to a gap between MS/MS data and the cancer genomics community. Here, we present a new search engine PepQuery, which does not require customized databases and allows quick and easy proteomic validation of genomic alterations. Methods: PepQuery takes as input a novel peptide, protein, or DNA sequence, or novel genomic features in the VCF, BED, or GTF file format, and the workflow includes five major steps: target peptide sequence preparation and initial filtering, candidate spectra retrieval and peptide-spectrum match scoring, competitive filtering based on reference sequences, statistical evaluation, and competitive filtering based on unrestricted modification searching. Results: We demonstrated high sensitivity and specificity of PepQuery in validating completely novel proteins, novel splice junctions, and single amino acid variants. We also showed that PepQuery is effective in removing false identifications reported by previous proteogenomics studies. PepQuery is available as a standalone application as well as a web application (http://www.pepquery.org) to which we have contributed. Conclusions: We have developed PepQuery, a peptide-centric search engine for novel peptide identification and validation. We demonstrated the sensitivity and specificity of PepQuery. We anticipate that PepQuery will significantly increase the usage of MS proteomics data in the cancer genomics community.
CDN-level co-occurrences of germline and somatic variants in cancer often lead to incorrect variant annotation and underestimated impact

**Introduction:** Cancer cells explore a broad mutational landscape, bringing the possibility that tumor-specific somatic mutations could fall in the same codons as germline single nucleotide variants (SNVs) and leverage incorrect annotation to produce mutations with a potential impact on protein function. While multiple, temporally consecutive mutations to the same codon have in the past been detected in the germline, this phenomenon has not yet been explored in the context of germline-somatic variant co-occurrences during cancer development. When these events occur, current somatic mutation detection methods are considered to be highly specific for the germline variant call, and are not in context and can potentially annotate the resultant amino acid change incorrectly. Since multiple changes to a codon are more likely to result in a stopgain or non-conservative amino acid change, such incorrect annotations are likely to underestimate the true impact of the variant on protein fitness. In this way, tumor-specific variants could be leveraging existing germline variants to produce mutations with larger effects on phenotype.

**Methods:** To assess the prevalence and impact of these events, and to identify whether these events undergo positive selection during tumorigenesis, we examined germline context at somatic mutation sites for 1395 patients across four tumor types (breast, skin, colon, and head and neck) representative of different points along the somatic mutation rate spectrum. For each patient, we compared their somatic and germline variant call files and identified in cis somatic variants that were within two nucleotides of a germline variant and predicted to impact the same amino acid as the germline variant in cancer genes. Variant impact was predicted using the Evolutionary Action (EA) method, which predicts impact of missense SNVs on protein fitness resulting from the amino acid substitution.

**Results:** We found 392 codon-level co-occurrences between somatic and germline variants, including 134 co-occurrences with known cancer genes. We found that while these events do not appear to be under obvious positive selection during tumorigenesis, the somatic variant call was not an accurate representation of the protein site in the majority of cases where these events occurred. When the germline context was considered, the amino acid changes were more accurately predicted and their predicted impacts on protein fitness were significantly larger.

**Conclusions:** We conclude that these events often lead to imprecise annotation of somatic variants and underestimated impact prediction on protein fitness.

### Targeting Protein Deglycosylation as a Novel Anticancer Approach

**Introduction:** Proteinostasis is an intricate balance between the synthesis and degradation of proteins and is a tightly regulated process in all eukaryotic cells. Interestingly, proteinostasis abnormalities associated with metastasis and carfizomib have shown that targeting protein quality control and homeostasis is a useful approach to eliminate cancer cells. This suggests that proteinase-mediated protein degradation, one of the well-known molecular components involved in proteinostasis, is crucial for cancer cells to sustain their viability and oncogenic signaling. Our group has extended our initial developmental biology studies of a genetic disease to studying the same gene involvement in cancer, and have discovered how this novel target, a glycosidase involved in proteasome-mediated protein degradation, may play a role in cancer formation and progression.

**Methods:** Initially, both gene mRNA and protein expression studies were performed to identify differentially expressed genes amongst several sets of cancer cell lines and their normal cell type counterparts. Utilizing Western Blotting we explored the expression of a differentially expressed protein in a multitude of cancer cell types, including pancreatic cancer, breast cancer, and melanoma, then evaluated its role in cancer biology for those cancer types using several molecular approaches like short hairpin RNAs (shRNAs) to knockdown the gene, Western Blotting to determine signaling pathways, and flow cytometry and MITT cell proliferation assays to assess the enzyme’s role in cell proliferation and cell death. **Results:** From global gene expression studies and protein analyses, we identified that there is a dramatic difference in expression patterns of this glycosidase gene and protein between normal cells and their cancer counterparts in pancreatic cancer, breast cancer, and melanoma. With focus on melanoma, short hairpin RNA knockdown studies have shown a significant decrease in expression and ATPase activity for multiple melanoma cell lines, whereas in a tumoral mouse model, expression is significantly upregulated in primary tumors. From our data, we have learned that the enzyme functions by targeting this particular glycosidase in melanoma cells and is mediated by pleiotropic anticancer responses. **Conclusions:** In future studies, as we continue to study the association between this enzyme and the death or survival of different types of cancer cells, we will pursue the design and synthesis of small molecules against this enzyme, then further test this protein deglycosylation route as a promising target for cancer therapy.
Cancer Biology

75

TRIM44 in quiescent multiple myeloma cells stabilizes HIF-1α by deubiquitination for niche control

Nami McCarty, The University of Texas Health Science Center at Houston; Z. Chen; T. Lin

Introduction: Multiple myeloma (MM) is an incurable B cell malignancy characterized by the proliferation of plasma cells within the bone marrow (BM) microenvironment. Despite progress in the treatment of MM, NM is one of the key factors of treatment outcome in MM. Our previous studies using PKH67 fluorescent tracers showed that MM heterogeneity was correlated with the presence of stem-like cancer cells (Chen et al., Blood, cover). This study was the first to demonstrate a quiescent MM cell niche and the effects of functional interactions between quiescent MM cells and the microenvironment on MM growth and progression. To delineate the molecular pathways involved in PKH+ MM cell functions, we performed gene profiling analyses. DNA profiling analyses of the PKH+ and PKH-CD138+ cells revealed a novel gene called the tripartite motif containing 44 (TRIM44). Results: A search of the integrated cancer microarray database (Oncomine) further revealed that TRIM44 gene expression was significantly upregulated in MM compared to normal or monoclonal gammopathy of undetermined significance (MGUS, a precursor stage of MM), suggesting that TRIM44 expression may play an oncogenic role, contributing to MM progression. TRIM44 silencing, using CRISPR-CAS9 led to MM cell death, indicating the critical role of TRIM44 in MM cell survival. TRIM44 up-regulation, using lentivirus-mediated targeting, rendered MM cells to be maintained in a quiescent status. This proliferative status was reversible when TRIM44 was down-regulated. TRIM44 over-expressing (TRIM44OE) MM cells were better equipped to compete with HSCs for niche factors and other niche components. Increased TRIM44OE-MM cell targeting suppressed HSC differentiation into leukocytes. Despite its role in promoting quiescence, TRIM44 up-regulation in MM increased bone destruction in xenograft mice, which resembles the human MM pathology. TRIM44-induced MM cell survival within the niche partly due to hypoxia-inducible factor (HIF-1α) stabilization by TRIM44, which decreases HIF-1α polyubiquitination and degradation by its deubiquitase activity. Conclusions: Our data unveil novel roles of quiescent MM cells in MM pathology and its relation to MM survival within a hypoxic niche. In addition, our data further support that TRIM44 plays a unique role in promoting the survival of quiescent MM cells in the BM by stabilizing HIF-1α.

76

Enhancer invasion shapes MYCN dependent transcriptional amplification in neuroblastoma

Devon Fitzgerald, Baylor College of Medicine; S. Rosenberg

Introduction: Amplification of the oncogenic basic helix-loop-helix transcription factor MYCN is a defining genetic feature of high-risk neuroblastoma. Despite clear functional information defining the oncogenic role of MYCN in this disease, the effect of MYCN on genome structure and function remains incompletely understood. More recently, using a super-resolution microscopy technique, the authors identified MEIS1 and MEF2C dependent regulatory elements in a MYCN-amplified line of human neuroblastoma cells. Additionally, they found that MYCN amplification and MYCN-dependent transcription are non-randomly distributed within the E. coli genome. We are currently using Gam-seq to identify mechanisms of DSB formation and localization in E. coli as a model for similar processes in cancer cells.

77

Genome-wide mapping of DNA double-strand breaks in Escherichia coli

Devon Fitzgerald, Baylor College of Medicine; S. Rosenberg

Introduction: Cancer is an evolutionary process fueled by genome instability. DNA double strand breaks (DSBs) are highly toxic to all organisms, and inactivate repair of DSBs can lead to a variety of genome alterations. In Escherichia coli, starvation stress and high-dose DNA damaging agents can promote genome instability by decreasing the fidelity of DNA double-strand break (DSB) repair. Importantly, stress-induced mutagenic break repair (MBR) generates point mutations and gross- chromosomal rearrangements near repaired DSBs and can generate clusters of closely-spaced mutations. Similar MBR mechanisms are observed in many other cancer genomes, and other clustered mutations are proposed to originate from MBR-like mechanisms, and probably occur close to the original DSB location. Thus, the genomic distribution of spontaneous DSBs may drive local mutation rates and alter the repertoire of mutations from which novel phenotypes can emerge. However, mechanistic drivers of spontaneous DSB formation in cells and their possible localization in genomes are poorly understood. Methods: We have developed and validated a method to map genomic distribution of DSBs. We are using ChiP-seq to map the genome-wide binding profile of Gam, a specific DSB-binding protein from bacteriophage Mu. We call this novel technique Gam-seq. Results: First, we show that Gam-seq enriches for DNA flanking an endonuclease-induced DSB. Next, we used Gam-seq to detect spontaneous DSBs in the E. coli genome. We find substantial regional differences in the relative frequency of spontaneous DSBs—DSB signal varies approximately 10-fold between different genomic regions, with relative hot- and cold-spots ranging in size from a few hundred to a few thousand basepairs. DSB signal correlates with gene orientation and transcription location. Conclusions: Increased recruitment of Gam onto non-randomly distributed sites within the E. coli genome. We are currently using Gam-seq to identify mechanisms of DSB formation and localization in E. coli, as a model for similar processes in cancer cells.

78

Structures of human double-stranded DNA break repair complexes

David Taylor, The University of Texas at Austin; Y. Zhou; A. Davis; T. Paull

Introduction: Genomes provide the blueprint for cells to function. The cell has evolved elegant pathways to repair damaged genomic DNA, and defects in these DNA-repair machines lead to genomic instability and cancer. Double-stranded breaks are the most deleterious types of DNA damage. These breaks occur frequently during DNA replication and can be repaired by exogenous DNA-damage inducing factors. These lesions can be repaired via non-homologous end joining or homologous recombination. The Mre11–Rad50–Nbs1 (MRN) protein complex is important for eukaryotic double-stranded break repair. MRN senses these breaks by binding DNA ends with high affinity. MRN then activates the DNA damage response. Ku70/80 competes for DNA ends with MRN and recruits the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to sites of damage to non-homologous end joining (NHEJ) to promote the repair of end joining repair pathway components are linked to cancers of the breast, lung, colon, and skin. Uncovering the molecular mechanism of double-stranded break repair is necessary to understand the biology of cancer and to provide new avenues for cancer therapies. We used both cryo-electron microscopy to directly visualize intermediate states in DNA double-stranded break repair in humans. Results: We have performed negative stain EM on MRN and shown it exists in a “closed” state. Additionally, initial class averages show MRN is stabilized by DNA binding and contain additional density for the Nbs1 protein. Excitingly, we have obtained class averages of a DNA-PKcs-Ku70/80 complex that clearly
show both the DNA-PKcs and Ku components. Conclusions: We are currently in the first-year of our work funded by a CPRIT Scholar award to D David Taylor. These initial results suggest that high-resolution structural information will be obtained for these two complexes. Structures of these intermediates will provide insights into MRN architecture and site-specific recognition of double-stranded breaks. Our studies on the dynamics of how DNA-PKcs-Ku70/80/86 remodels MRN and how these complexes can undergo conformational structural rearrangements to bridge the two DNA ends for repair. These structural snapshots will provide the mechanistic basis for NHEJ.

79

CPRIT Grantee Poster Session A

Dominant-negative SMARCA4 (BRG1) mutations induce convergent effects on the enhancer accessibility landscape H. Courtney Hodges, Baylor College of Medicine

Introduction: Mutation of SMARCA4 (BRG1), the ATPase of BAF (mSWI/ SNF) and PBAF complexes, contributes to a range of malignancies and neurologic disorders. Here we investigated the effects of dominant-negative SMARCA4 disease mutations on BAF complex dynamics and genome-wide accessibility. Methods: We used integrative techniques, including bioinformatic analysis of tumor sequencing studies, structural biology, epigenomics, and live-cell imaging to interrogate the altered mechanisms induced by heterozygous missense mutations of SMARCA4. Results: By constructing a homology model of SMARCA4 on crystal structures of related Snf2-like ATPases, we discovered that cancer mutations target conserved, functionally important surfaces and disrupt key steps in the mechanochemo cycle of remodeling. Despite distinct modes of inactivation, heterozygous mutations lead to common changes of the open chromatin landscape at thousands of sites across the genome in mESCs. To our surprise, loss of accessibility did not occur at sites that accumulated PRC1, but was enriched at active enhancers, where it coincided with loss of H3K27ac but not H3K4me1. Heterozygous SMARCA4 mutation altered accessibility at hundreds of sites identified as superenhancers in many different tissue types. Losses were especially enriched in transcriptionally active “A compartments.” Analysis of gene expression using RNA-seq showed increased expression of Myc and its target genes. Conclusions: Together, our data suggest that disruption of enhancer accessibility is likely to be a key source of altered function in SMARCA4-mutated disorders in a wide variety of tissues.

80

CPRIT Grantee Poster Session B

Evaluating transcription factor networks as targets for the treatment of neuroendocrine tumors Karina Pozo, The University of Texas Southwestern Medical Center; R. Kollipara; J. Minna; A. Gazdar; J. Johnson

Introduction: Achaete-scute homolog 1 (ASCL1) is a transcription factor that is highly expressed in neuroendocrine tumors (NETs) including, gastrointestinal carcinoids, medullary thyroid carcinoma and neuroendocrine prostate cancer. It is overexpressed in most but not all small cell lung cancer (SCLC) tumors and cell lines. ASCL1 expression is particularly critical for the proliferation of some gastrointestinal carcinoids and SCLCs. Inhibiting ASCL1 transcriptional activity may thus be a valid therapeutic strategy for these NETs. However transcription factors (TFs) have been historically difficult to target. Given that TFs belong to complex regulatory networks, we propose to identify and target multiple components within an ASCL1-transcriptional network rather than ASCL1 alone. We have previously detected ASCL1-bound genomic regions associated with the active chromatin epigenetic mark, H3K27Ac in SCLC cells. Here we report the identification of an ASCL1-containing transcriptional network in SCLC cells and evaluate its targeting by the transcriptional inhibitor, mithramycin. Methods: Chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) were performed using immunoprecipitating chromatin from NCI-H2107 and NCI-H69 SCLCs (SCLC cell lines) and NC1-1H3, H2812, and H292 cells which are SCLC cell lines. ChIP-seq libraries were sequenced on an Illumina High-Seq2000. siRNA transfections, immunoblotting and MTS-cell proliferation assays were conducted using standard procedures. Results: 82 overlapping TF genes, including lineage-specific TF genes for ASCL1, Forkhead box protein A2 (FOXA2) and Nuclear factor A2 (NFIB) were identified and associated with the active chromatin epigenetic marks H3K27Ac in SCLC cell lines. This suggests ASCL1, FOXA2 and NFIB may belong to the same transcriptional network. siRNA-mediated knock-down of ASCL1, FOXA2, NFIB, and Nuclear factor A2 (NFIB) was performed in SCLC cell lines, implicating ASCL1 as a transcriptional regulator of FOXA2 but not NFIB. Mithramycin stops cell proliferation and reduces ASCL1, FOXA2 but not NFIB protein levels. Conclusions: Our studies identify the beginning of a transcriptional network necessary for SCLC proliferation in which ASCL1 regulates FOXA2. Targeting multiple TFs within a network with mithramycin can stop cell proliferation and as such suggests a therapeutic strategy for NETs. Because of the importance of NFIB in mediating metastatic behavior of SCLC, these data indicate approaches other than targeting ASCL1 and use of mithramycin will be needed to target NFIB.

81

CPRIT Grantee Poster Session A

Therapy-induced apoptosis stimulates cancer cell proliferation via WNT-containing apoptotic bodies Stephen Wallin, The University of Texas MD Anderson Cancer Center

Introduction: The ability to prevent tumor repopulation after anticancer treatments has been a significant barrier to reducing morbidity and mortality of malignant tumors. Standard chemotherapeutic agents induce the death of rapidly dividing cells. Dying cells can provide instructive cues that influence the behaviors of surrounding cells, yet the mechanism for how apoptosis-stimulated proliferation of normal cells is not well understood. Here we show that treatment with chemotherapeutics promotes caspase-dependent production of WNT-containing apoptotic bodies that stimulate cancer cell proliferation. Methods: We used live imaging and tissue analysis to characterize apoptosis of MDA-MB231 breast cancer cells after exposure to different chemotherapeutics. Transcript levels for WNT pathway members were analyzed by quantitative real-time PCR. Protein levels and localization within the apoptotic cells were determined by immunofluorescence confocal microscopy. Breast cancer-derived apoptotic bodies were isolated by differential ultracentrifugation and treated with fluorescent labeled anti-WNT16 antibody in an electron microscopy. Time lapse microscopy was used to follow fluorescently labeled apoptotic bodies after addition to healthy cultures. Results: Time lapse microscopy of human breast cancer cells after treatment with different chemotherapeutic agents revealed highly regulated, distinct morphological processes during apoptosis and subsequent production of apoptotic bodies. We identified specific WNT molecules induced in dying cells that become enriched in the apoptotic bodies. Purification and addition of the breast cancer-derived apoptotic bodies to healthy cultures stimulated proliferation. Further, live imaging revealed cancer cells that engulf the apoptotic bodies go on to divide. Inhibition of either apoptosis or WNT signaling eliminated the apoptosis-induced cell division. Conclusions: This study presents a novel mechanism by which dying cancer cells communicate with their healthy neighbors and induces proliferation. We have identified apoptotic proteins induced by damage in apoptotic cells, and characterized a novel mechanism by which apoptotic cells transfer signaling molecules and induce localized proliferation in neighboring cells. Thus, apoptotic body-mediated regrowth may provide a possible mechanism for tumor repopulation and treatment resistance.

82

CPRIT Grantee Poster Session B

Chemical induction of Krüppel-Like Factor 4 shows anti-leukemic properties in Acute Myeloid Leukemia Andrew Lewis, Baylor College of Medicine; C. Park; A. Peng; D. Peng; C. Sun; G. Yang; R. Kollipara

Introduction: Acute Myeloid Leukemia (AML) continues to evade effective therapeutic advances indicated by the lack of novel treatment approaches over the past 30 years. Transcript level repression of KLF4 in AML patients across subtype classifications and genetic abnormalities suggests potential tumor suppressor function. Our group has also demonstrated the importance of this gene in restraining cell cycle progression of leukemias and T-cells by preventing the activation of kinase pathways. We hypothesized that KLF4 inhibits cell cycle progression and survival in human AML cells. Methods: Using human AML cell lines, we determined KLF4 protein, then by genetic and chemical methods examined the effect of restoring KLF4 expression. Results: In order to test this hypothesis, we began by detecting basal KLF4 protein levels in a panel of AML cell lines. NB4, MonoMac-6, SKM1, and NOMO-1 cells had non-detectable KLF4 protein levels when compared to lymphobastoid cells used as non-leukemic controls. In order to study pharmacological activation of KLF4, we utilized the chemical compound APTO-253, which had previously been reported to induce KLF4 expression in human colon cancer cells. Immunoblot analysis confirmed induction of KLF4 in 3 AML cell lines following treatment with this compound, but not in K562 cells. In the panel of AML cell lines, APTO-253 treatment resulted in apoptosis in 5 out of 6 AML cell lines with IC50 values ranging from 1 to 5 µM at 24 hours. APTO-253 treatment did not significantly induce apoptosis in non-AML control cell line K562 at doses up to 40 µM. Analysis of DNA content by propidium iodide staining revealed G1 cell cycle arrest and Annexin V staining revealed induction of apoptosis. In order to account for potential effects which were not the result of KLF4 induction, we transduced NB4 cells with a retroviral vector driving ectopic expression of KLF4 or a control empty retroviral vector. KLF4 overexpressing cells exhibited drastic apoptosis and G1 cell cycle arrest, similar to results observed in the presence of APTO-253. To test whether KLF4 expression might cooperate with chemotherapeutic agents via its known regulation of apoptotic pathways, we treated cells
with a combination of APTO-253 and the chemotherapeutic compound daunorubicin. Treatment with APTO-253, however, did not enhance cytotoxicity in assays, but the cells are transformed by RAG-2. Altogether, chemical and genetic restoration of KLF4 expression results in selective cytotoxicity, apoptosis, and cell cycle arrest in AML cells. This finding supports the possibility of therapeutic approaches for AML involving KLF4 induction.

83

CPRIT Grantee
Poster Session A
Optimization of Gene Editing Technology for Generation of DEAR1 Knockout in Human Breast Cancer Cells Nanyue Chen, The University of Texas M.D. Anderson Cancer Center; Z. Huang; U. Le; S. Balasenthil; C. Evers; D. Dutra; A. Kiliaris
Introduction: Ductal carcinoma in situ (DCIS) is an early, pre-invasive form of breast cancer which, if untreated, progresses to invasive ductal carcinoma (IDC) in approximately 40% of cases. Predictive and prognostic markers are critically needed to stratify DCIS with a heightened risk of progression to IDC for which more aggressive surveillance and treatment might be warranted, as well as individuals with favorable prognosis, who might be spared rigorous therapeutic regimens. Our laboratory has discovered a novel tumor suppressor DEAR1 (Ductal Epithelium Associated Ring Chromosome 1, annotated as TRIM62). DEAR1 is mutated or homozygously deleted in breast cancer and is downregulated in IDC. DEAR1 is encoded by a pseudogene and functions as a negative regulator of TGFbeta signal transduction by binding to and ubiquitinating SMAD3, the major effector of TGFbeta-mediated Epithelial-Mesenchymal Transition (EMT). Therefore, the mutation or loss of function of DEAR1 is an important model for DCIS progression. To investigate if loss of DEAR1 contributes to progression from DCIS to IDC, we developed a strategy for gene editing to knockout or edit mutations in DEAR1 in two different breast model systems. Methods: Two gene editing technologies, i.e., TALENS and CRISPR-mediated (Cas) systems were developed to knock out (KO) DEAR1 alleles in the breast cancer cell line DCIS.COM and in the immortalized human mammary cell line 76E-E6. Results: Exhaustive studies were performed to develop DEAR1 KO clones in DCIS.COM and 76E-E6 cells using both CRISPR and Talen technology. We further validated these KO clones at the DNA and RNA level. At the DNA level, genotyping by electrophoresis and droplet PCR confirmed that there is no wild type (WT) DEAR1 sequence in tested KO clones. At the mRNA level: we performed regular RT-PCR, TA cloning and Sanger sequencing and verified the INDEL of most KO clones. Furthermore, we performed RACE-Smart technique and excluded any trace of WT sequence in RNA of KO clones. However, DEAR1 protein expression was still present by westerns despite convincing data at the genotypic and RNA level. We are using 2D-DIGE and mass-spectrometry assays to identify proteins of similar size as DEAR1 that might be recognized by our antibody as well as we are generating a monoclonal antibody as a future target. Conclusions: We established DEAR1 KO at the DNA and RNA confirm that we have successfully knocked out DEAR1. Experiments are underway to definitively determine whether the DEAR1 antibody recognizes additional proteins besides DEAR1.

84

CPRIT Grantee
Poster Session B
Hyperspectral expansion microscopy using SERS nanoparticles Camille Artur, University of Houston; T. Womack; F. Zhao; J. Ejriksen; D. Mayench; W. Shih
Introduction: Newly developed expansion microscopy techniques offer a dramatically different approach to super-resolution biomedical imaging by physically expanding tissue such that spatial features smaller than the diffraction limit can be resolved on a conventional fluorescence microscope. With minimal changes to well established immunostaining protocols, tissue sections go through an isotropic three-dimensional expansion which preserves their structural information. This technique nevertheless suffers from significant signal loss caused by number of labels per focal volume, and is inherently limited in terms of multiplexing. We propose the use of functionalized gold Raman nanoparticles labeled with a monolayer of a dye, which are partially dehydrogenated in near-infrared dyes, protected by a passivation layer and further conjugated with streptavidin. 10μm mouse brain sections are stained against the NeuN antibody, biotinylated secondary and the SERS labels. Slides are embedded in a medium containing polyethylene glycol which can swell by a factor of 5 upon addition of water. Tissue sections are imaged pre- and post-expansion on a dark-field microscope then on a home built line-scan Raman microspectrometer with 785 nm excitation. Results: The SERS tags prove their effectiveness and specificity in labeling NeuN antigens on the brain sections pre- and post-expansion. Unlike traditional fluorophores, the staining of neurons is visible on conventional microscopes. Pre-expansion, the stained structures are purple in brightfield and yellow-red under darkfield contrast. The contrast is maintained after tissue expansion. Altogether, chemical and genetic restoration of KLF4 expression results in selective cytotoxicity, apoptosis, and cell cycle arrest in AML cells. This finding supports the possibility of therapeutic approaches for AML involving KLF4 induction.

85

CPRIT Grantee
Poster Session A
The role of Ductal Epithelium Associated Ring Chromosome 1 (DEAR1) in the regulation of stem/progenitor cell properties Min Li, The University of Texas M.D. Anderson Cancer Center; N. Chen; S. Balasenthil; A. Kiliaris
Introduction: Breast cancer is the most commonly diagnosed cancer and second-leading cause of cancer-related deaths in women in America. A quarter of lesions diagnosed annually are ductal carcinoma in situ (DCIS), one of the earliest pre-cancerous lesions of invasive ductal carcinoma (IDC). Without therapeutic intervention, 30–40% of DCIS cases can progress to IDC. Understanding the mechanisms regulating progression from DCIS to IDC would help identify biomarkers to stratify DCIS patients at higher risk of progression or recurrence. Consistent with literature suggesting breast cancer stem cells (CSCs) disseminate primarily through the blood, we developed the epithelial-mesenchymal transition (EMT) program. DEAR1 is a tumor suppressor gene which is mutated, undergoes loss of heterozygosity in breast cancer, and is downregulated in DCIS lesions. DEAR1 also regulates acinar morphogenesis and cell polarity, and is a negative regulator of TGF-beta-driven EMT by binding to and ubiquitinating SMAD3, thereby limiting the amount of SMAD3 available to activate an EMT signature. Overexpression of EMT master regulators, or exposure to TGF-beta in immortalized human mammary epithelial cells (HMECs), results in mammosphere formation and breast stem cell markers, thus linking the EMT process to acquisition of stem cell characteristics. Methods: Stable lentiviral shRNA knockdown, in vitro mammosphere assay, cytospin, immunofluorescence, western blot analysis, and real-time quantitative PCR were performed. Results: DEAR1 knockdown in immortal HMECs resulted in a significant enhancement of primary mammosphere formation and growth compared to controls, suggesting that DEAR1 may regulate stem/progenitor cell properties; this effect was greater when cells were exposed to TGF-beta. To determine if DEAR1 regulates stem cell properties through regulation of SMAD3 levels, DEAR1-KD/HMECs were exposed to TGF-beta. To determine if DEAR1 regulates stem cell properties, we measured differences in stem cell properties between controls and DEAR1-KD/HMECs. We observed upregulation of SNAI2 and ZEB1, master EMT and stem cell regulators, in DEAR1 knockdown HMECs. Conclusions: Loss of the tumor suppressor/polarity regulator DEAR1 promotes stem cell properties in part through the TGF-beta-SMAD3 axis. These mechanisms governing acquisition of the stem cell properties may contribute to understanding how DCIS progress to IDC.

86

CPRIT Grantee
Poster Session B
Role of the perinuclear protein translation in cancer cell chemoresistance Tattym Shaiken, Peri-Nuc Labs LLC
Introduction: Life of eukaryotic cells is associated with compartmentalization of essential functions. One compartment about which little is known is the perinuclear region or perinucleus. The perinuclear region is surrounded by a complex of intermediate filaments that are partially surrounded by an inner nuclear membrane and contains ribosomes and regulators of protein biosynthesis. Most protein biosynthesis takes place in the cytoplasm and involves “floating” and ER-bound ribosomes. Nuclear membrane-bound ribosomes located in the perinuclear space are considered as cytoplasmic ribosomes. Methods: We have isolated nascent ribosomes and investigated regulation of perinuclear protein translation. Results: Eukaryotic initiation factor 4E3 (eIF4E3) cap binding protein that does not bind to 4E binding proteins (4E-BP proteins), initiates perinuclear protein synthesis when eIF4E1-dependent protein translation is inhibited. Inhibition of eIF4E1-dependent protein translation by mechanistic Target of Rapamycin (mTOR) kinase inhibitor increased the level of eIF4E3 in the cytoplasm producing a slow-
moving band of elf4E3 that appeared in the perinucleus. Perinuclear protein translation primarily involves light polypeptides for protein synthesis. Perinuclear protein translation correlates with the presence of the nucleolus that was manifested as nucleolar hypertrophy. Suppression of other cytoplasmic signaling pathways also result in upregulated perinuclear protein synthesis, translational reprogramming and nucleolar hypertrophy. Perinuclear ribosomes appear to be separate from the cytoplasmic ribosomes and regulate the translation of the proteins needed to maintain the nucleolus in the proximity of the nucleus. Conclusions: Our results indicate that nutrient sensing protein translation and cell survival protein translation can be separated and it is mTOR-independent. Perinuclear protein translation is essential for ribosome biogenesis in stress. This newly discovered secondary pathway, perinuclear protein translation, thus makes cancer cells less dependent on the cytoplasmic signaling pathways and can support sustained proteome imbalance. Many chemotherapeutic agents directly or indirectly are designed to downregulate protein synthesis. In stressful conditions, cells utilize perinuclear protein synthesis which remains active even when cytoplastic protein synthesis is reduced or inhibited. Cancer cells can also use glycolysis as their primary energy source for the perinuclear protein translation (the Warburg effect). Suppression of the perinuclear protein translation is a new target that eliminates an escape mechanism that allows cancer cells to become resistant to important chemotherapy agents.

87 Poster Session A
Structural and molecular mechanisms of Ca2+-mediated activation of estrogen receptor-alpha by calmodulin Yongzhong Zhang, The University of Texas Health Science Center at El Paso; D. Scatch; J. Amers
Introduction: Estrogen receptor alpha (ER-a) is a nuclear hormone receptor that controls selected genes, regulates proliferation and differentiation of target tissues (e.g. breast) implicated in breast cancer. Binding of estrogen hormone to ER-a induces receptor homodimerization and activates its transcriptional function. Calcium-dependent activation of ER-a is also mediated by calmodulin (CaM) via the ubiquitin-proteasome pathway. The Ca2+-induced binding of CaM to ER-a has important implications for breast cancer. Despite a wealth of information for both ER-a and CaM, the detailed molecular mechanisms underlying this regulation remain to be elucidated. A clear molecular picture of calcium-dependent ER-a signaling is required to develop better therapeutic modalities. Methods: This work takes a multi-disciplinary approach incorporating NMR structural biology techniques for 3D structure determination of ER-a/CaM (2:1) complex, in parallel with the detailed analysis of ER-a to provide in vivo evidence that bolsters the structure.

88 Poster Session B
Metabolic phenotypes reveal novel therapeutic targets in KRAS/LKB1 mutant non-small cell lung cancer Ralph DeBerardinis, The University of Texas Southwestern Medical Center; J. Kim; K. Li; K. Huffman; E. Choi; D. Castrillon; B. Chen; J. Kim; J. Xu; J. Minna
Introduction: Genetic heterogeneity in cancer generates genotype-specific metabolic preferences which may be exploited to kill malignant cells. In non-small cell lung cancer (NSCLC), concomitant oncogenic mutations in KRAS and loss of the tumor suppressor LKB1 specify an aggressive tumor phenotype in both mice and humans. Because KRAS and LKB1 independently regulate metabolism in cancer cells, we studied whether the metabolic phenotypes were significantly changed when both mutations occurred together. Methods: We performed metabolomics in cell lines and tumors with mutations in KRAS alone (K) or both KRAS and LKB1 together (KL) to identify emergent metabolic properties. Transcriptome analysis was used to identify mechanisms to explain metabolic dysregulation in KL cells, and loss of function studies were used to assess candidate liabilities in cell lines and xenografted tumors. Results: Metabolomics in human cell lines and tumors from both KRAS and LKB1 mutant non-small cell lung cancers revealed widespread alterations in nitrogenous metabolites, particularly amino acids and nucleotides. Expression studies revealed that human KL cell lines and tumors express high levels of the urea cycle enzyme, carbamoylphosphate synthase-1 (CPS1), which condenses ammonia and ornithine to form citrulline and arginine. CPS1 is induced by cytosolic calcium, and alanine aminotransferase (ALT) is strongly expressed in the liver and other tissues, where CPS1 is also localized. CPS1 is further regulated by calmodulin (CaM) via the ubiquitin-proteasome pathway. Our results also indicate that alanine aminotransferase (ALT) is strongly expressed in the liver and other tissues, where CPS1 is also localized. CPS1 is further regulated by calmodulin (CaM) via the ubiquitin-proteasome pathway. Conclusions: Our results indicate that alanine aminotransferase (ALT) is strongly expressed in the liver and other tissues, where CPS1 is also localized. CPS1 is further regulated by calmodulin (CaM) via the ubiquitin-proteasome pathway. Conclusions: Our results indicate that alanine aminotransferase (ALT) is strongly expressed in the liver and other tissues, where CPS1 is also localized. CPS1 is further regulated by calmodulin (CaM) via the ubiquitin-proteasome pathway.
of HNF1alpha in pancreatic cancer. Conclusions: We conclude that HNF1alpha is an oncogenic transcription factor and could serve as a potential therapeutic target to treat pancreatic cancer.

91 Poster Session A
Deregulated PRAJA1-TGF-beta signaling pathway in Beckwith-Wiedemann syndrome-associated liver tumorigenesis Jian Chen; The University of Texas M.D. Anderson Cancer Center; M. Hung; X. Su; B. Fang; E. Haussler; D. Lee

Introduction: Beckwith-Wiedemann syndrome (BWS) is a congenital stem cell disorder characterized by a defective developmental program resulting in enlarged organs. BWS is associated with an 800-fold increased risk of childhood neoplasms, including Wilms tumor, hepatoblastoma, and other childhood cancers. The molecular etiology of BWS is complex and poorly understood. Among all the mechanisms, specific pathways drive BWS-associated liver tumorigenesis are unclear. Spb1n1+/-/Smad3d+/+ mice (Spb1n1, a key adaptor for TGF-beta/Smad3 pathway) with defective TGF-beta signaling develop multiple tumors that are phenotypically similar to those in BWS, suggesting that disrupted TGF-beta signaling may be responsible for driving BWS and BWS-associated malignancies. Therefore, restoring TGF-beta tumor suppressor function would be a potentially effective therapy and a new research direction for BWS-associated cancers. We further sought to determine detailed mechanism by which a defective TGF-beta pathway triggers liver cancer development. We asked: (1) Performed on RNA-seq data analysis from TCGA liver cancer database. (2) Patient-derived induced pluripotent stem cells (iPSCs) were generated from BWS patients. (3) Immunochemistry analyses were performed on BWS-induced treated cells (4) TGF-beta induced E3 ligase PRAJA1 phosphorylation assays were performed in hepatoblastoma cells. Results: (1) Whole-transcriptome RNA sequencing of liver cancer samples from TCGA display that the defective TGF-beta signaling is associated with poor survival. The TGF-beta-pathway-related E3 ubiquitin ligases, PRAJA1, WWPT1/WWP2, deubiquitinases (DUBs), and UCHL5 are the most commonly altered genes in liver cancer patients. (2) The levels of PRAJA1 are negatively correlated with Sptbn1, Smad3 or CTGF in BWS-associated tumors. (3) PRAJA1 is increased in liver cancers and dramatically induces liver stem cells to develop into liver tumor-initiating cells. (4) Inhibition of PRAJA1 leads to high levels of apoptosis and reduction of liver cancer tumorigenesis. (5) TGF-beta induces PRAJA1 tyrosine/serine phosphorylation and PRAJA1 may have a negative-feedback role on the TGF-beta pathway. Conclusions: Based on our current preliminary data, we demonstrated the critical tumor suppressor role of the TGF-beta pathway in BWS-associated liver tumorigenesis. We focus on targeting defective TGF-beta signaling in liver cancer development and deeply investigate the detailed mechanisms by which PRAJA1 negatively regulates TGF-beta signaling in liver cancers. Completion of this study should provide valuable insight into the development of more effective targeted treatment for BWS-associated liver cancer patients.

92 Poster Session B
Telomerase Substrate Precursor 6-Thio-2-Deoxyguanosine Overcomes Cancer Cell Line Targeted Therapy Resistance and Multi-drug Chemotherapy Resistance (TC-PTP) attenuates skin carcinogenesis induced by chemical regimens, the ligand-dependent activation of PTKs and induces PTP inactivation. Introduction: Lung cancer patients with advanced disease are treated with standard chemotherapies and/or targeted therapies as first- and second-line therapies. However, these therapies almost universally fail due to tumor heterogeneity leading to intrinsic or acquired drug resistance. Therefore, it is important to seek new approaches to target multi-drug resistance. Since ~90% of primary human tumors express the ribonucleoprotein enzyme telomerase, but not most somatic tissues, telomerase is a highly attractive, almost universal, target for anticancer therapy. Recently, we reported that the nucleoside, 6-thio-2-deoxyguanosine (6-thio-dG), is very effective in rapidly killing telomerase positive cancer cells in vitro and in vivo, but not normal telomerase silent cells, with minimal cytotoxic side effect to normal tissues. In this study, we tested the effects of 6-thio-dG in immunocompetent syngeneic xenograft and genetically engineered mouse models of lung cancer and on a large series of human non-small cell lung cancer cell lines including those selected for multi-drug resistance. Methods: Colony formation assay, cell viability assay, RNA sequencing, xenograft mouse model, syngeneic mouse model, genomics. Results: We found that erlotinib, paclitaxel/carboplatin and gemcitabine/cisplatin resistant cells were sensitive to 6-thio-dG in vitro and/or in vivo. In addition, we tested the anticancer effect of 6-thio-dG in a syngeneic immunocompetent xenograft mouse model and showed that the addition of 6-thio-dG to gemcitabine and cisplatin combination therapy caused more tumor shrinkage compared to doublet therapy alone without increasing toxicities. We used a genetically engineered mouse model of lung cancer (K-RAS LA1) to test the effect of 6-thio-dG and found that treatment of tumors in one year old K-RAS LA1 mice were significantly smaller with just two weeks of treatment with 6-thio-dG. In addition, we tested 6-thio-dG on a large panel of well characterized non-small lung cancer cell lines and observed 73 out of 77 NSCLCs were sensitive. We further demonstrated that the 4 resistant NSCLC lines clustered together (RNAseq). These results suggest that tumors that may not respond to 6-thio-dG. Conclusions: 6-thio-dG is a novel and highly effective approach to prolong disease control of therapy-resistant tumors in almost all lung cancer patients.

93 Poster Session A
Characterizing the efficacy of anticancer drug treatment using mathematical models Hope Murphy, Texas Christian University; E. Szemore; A. Naumov; H. Dobrovolny

Introduction: In order to determine correct dosage of chemotherapy drugs, the effect of the drug must be properly quantified. There are two important values that characterize the effect of the drug: Emax is the maximum possible effect from a drug, and IC50 is the drug concentration where the effect diminishes by half. Currently, the technique used to measure these quantities gives estimates of the values that depend on the time at which the measurement is made. We use mathematical modeling to test a new method for measuring Emax and IC50 that gives estimates independent of measurement time. Methods: We performed on human colon cancer tumor xenograft mouse model of lung cancer and examined two assumptions for the effect of doxorubicin: first assuming that doxorubicin reduces growth rate, and second assuming that it reduces the maximum number of cells. Results: Our method produced IC50 estimates similar to estimates derived using current techniques. Our calculations show that the Emax for doxorubicin in MCF-7 cells under the assumption of reduced growth rate, is 0.500, and the IC50 is 210 nM. Under the assumption that doxorubicin reduces the maximum number of cells, we found an Emax of 92% and an IC50 of 190 nM. Conclusions: We determined values for Emax and IC50 using mathematical models under two assumptions: that the drug reduces growth rate, or maximum number of cells. The IC50 was similar in both cases, but for doxorubicin it seems to be better at reducing the maximum number of cells as opposed to reducing the growth rate. This work is intended to characterize the efficacy of anticancer drug treatments and determines the correct doses before trying those in patients to get the most effective therapeutic treatment.

94 Poster Session B
TC-PTP deficiency in mouse epidermis promotes UVB-induced keratinocyte cell survival through the regulation of VEGFR2 signaling Dae Kim, The University of Texas Rio Grande Valley; M. Kim; J. Lim; L. Sizemore; A. Naumov; H. Dobrovolny

Introduction: Ultraviolet B radiation (UVB) exposure can contribute to the development of skin cancer by modulating protein tyrosine kinase (PTK) signaling. It has been suggested that UVB radiation increases the ligand-independent activation of PTKs and induces PTP inactivation. Our recent studies have shown that T cell protein tyrosine phosphatase (TC-PTP) regulates skin carcinogenesis induced by chemical regimens, which indicates its critical role in the prevention of chemically-induced skin cancer. In the current work, we report that activation of TC-PTP in vitro leads to increased keratinocyte susceptibility to UVB-induced apoptosis via the downregulation of vascular endothelial growth factor receptor 2 (VEGFR2) signaling. Methods: We generated immortalized TC-PTP-deficient (TC-PTP KO) keratinocytes from epidermal-specific TC-PTP KO mice. Results: Immortalized TC-PTP-deficient (TC-PTP KO) keratinocytes showed increased cell survival against UVB-induced apoptosis which was associated with increased expression of a UVB-induced phosphatase. Treatment of TC-PTP KO keratinocytes with the VEGFR2 inhibitor, SU5416 and ZD6474, reversed this effect and significantly increased cell death after UVB irradiation in comparison with untreated TC-PTP KO keratinocytes. Immunoprecipitation analysis using the TC-PTP substrate-trapping mutant TCPTP-D182A indicated that TC-PTP directly interacts with VEGFR2 to dephosphorylate it and their interaction was stimulated by UVB irradiation. Following UVB-mediated VEGFR2 activation, the level of c-Jun N-terminal kinase (JNK) phosphorylation was also significantly increased in TC-PTP KO keratinocytes compared to controls. Knockdown of VEGFR2 in TC-PTP KO keratinocytes with the JNK inhibitor SP600125 significantly increased apoptosis after UVB irradiation, confirming that the effect of TC-PTP on UVB-mediated apoptosis is regulated by VEGFR2/JNK signaling. Conclusions: Our results suggest that TC-PTP plays a protective role against UVB-induced keratinocyte cell damage by negatively regulating VEGFR2-dependent cell survival signaling.
**Poster Session A**

### Tgf beta-dependent, transcriptional regulation of ARF in human cancer cells

**Yen-Ting Liu, The University of Texas Southwestern Medical Center**

**Introduction:** Disruption of the CDKN2A locus at chromosome 9p21 is one of the most common events in human cancer. Two proteins, p16Ink4a and p14ARF (p19Arf in the mouse), are encoded in this locus and function independently as tumor suppressors. The INK4A and ARF genes are usually deleted or silenced due to methylation or loss proximity at 9p21, but in some settings, their transcriptional control can be uncoupled. Study of their differential regulation, therefore, is important to understand disparate pathways in specific cancerous transformation events. Our laboratory team previously unveiled a new pathway in which Tgf beta induces ARF, but not Ink4a, during mouse embryo development. This is intriguing because Tgf beta signaling pathways are often derailed in cancer development or progression. Numerous effectors have been proposed in the Tgf beta-driven cancer suppression. Here, we are exploring the Tgf beta-ARF pathway human cancer lines.

**Methods:** We utilized computational approaches in secondary analyses of public ChIP-seq databases to identify human cell lines with intact ARF gene and open chromatin to allow basal RNA Polymerase II binding at the promoter. We directly studied regulation of ARF expression in response to Tgf beta under different conditions through qRT-PCR and Western blotting. We used molecular biology tools to investigate how transcriptional and RNA polymerase II occupancy at the ARF promoter is influenced by Tgf beta in human cancer cell lines.

**Results:** Our studies revealed Tgf beta-dependent induction of ARF transcription in HeLa cells, and the induction slowed proliferation in vitro. The induction of ARF was dependent on SMAD3 and SMAD4 activation in HeLa cells in response to Tgf beta, SMAD4 and SP1 were recruited to the ARF promoter. However, Tgf beta-induction did not further recruit RNA polymerase II to the promoter region, which appeared to be pre-loaded at the transcription start site in HeLa cells, in contrast to early passage mouse embryo fibroblasts. Even though SMAD3 and SMAD4 recruit RNA polymerase II to Tgf beta, SMAP5 does not appear to be pre-loaded at the transcription start site in HeLa cells, in contrast to early passage mouse embryo fibroblasts. Even though SMAD3 and SMAD4 recruit RNA polymerase II to Tgf beta, SMAP5 does not appear to be pre-loaded at the transcription start site in HeLa cells.

**Conclusions:** We report a previously unrecognized role for Tgf beta to induce the expression of the ARF tumor suppressor in human cancer cell lines. Our data suggest that Tgf beta signals to recruit RNA polymerase II to the promoter machinery at ARF promoter. Ongoing experiments using CRISPR/Cas9-mediated genome editing are further defining enhancer elements that are critical in this process.

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**Poster Session B**

### Stromal Hedgehog pathway activation suppresses growth and metastasis of lung adenocarcinoma

**Sahba Kasiri, The University of Texas Southwestern Medical Center**

**Introduction:** Aberrant activation of the hedgehog (Hh) signaling pathway, a crucial developmental pathway, drives the tumor growth of Gorlin-type cancers. However, recent data suggest that paracrine activation of the pathway is tumor suppressive rather than oncogenic in sporadic epithelial cancers. The role of the pathway in non-small lung cancer is poorly understood. Thus, we explored the role of stromal Hh pathway activation in growth and metastasis of lung epithelia. Methods: Human lung adenocarcinoma cell lines were used to probe SHH mRNA and protein expression. Co-culture of high SHH expressing cell lines with murine embryonic and lung fibroblasts were used to confirm and probe the role of paracrine SHH expression on the growth of lung cancer cells. The in vivo role of paracrine SHH was tested using autochthonous lung cancer models with conditional KRASG12D/activation, p53 loss, and SHH loss impaired as evidenced by RNA-seq analysis. Remarkably, silencing SIRT1 in LNCaP cells reduced AR signaling as evidenced by decreased levels and expression of AR target genes (PSA, TMPRSS2, FKBPs) and secreted levels of PSA. Interestingly, SIRT1 KD reduced PSA reporter activity under both normal physiological and androgen deprivation growth conditions with no significant impact on nuclear or cytosolic levels of AR. More importantly, silencing SIRT1 increased sensitivity to growth under androgen deprivation conditions. However, knockdown of SIRT1 in 22Rv1 cells has no significant impact on AR signaling as well as expression of AR variants, but leads to morphological changes in part through modulation of EMT program.

**Conclusions:** Taken together, these data indicate that SIRT1 plays a regulatory role in PCA progression to castrate resistance by altering AR transcriptional network, independent of classical AR signaling. Thus, our study identifies previously uncharacterized role for SIRT1 in promoting castrate resistance and sustaining cell survival, providing new opportunities to develop anti-cancer therapeutic approaches for treatment of patients with advanced stage PCA. Supported by CPRIT RP 150166 (APK).

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**Poster Session B**

### The role of exosome subpopulations in glioblastoma progression

**Amanda Haltom, The University of Texas M.D. Anderson Cancer Center**

**Introduction:** Exosomes (Exos) are heterogeneous, naturally arising cell-derived nanovesicles that are proposed to play a role in intercellular communication to maintain homeostasis and response to stress. This may be achieved through the complex heterogeneity of these nano-sized vesicles, which can be demonstrated by the presence of tetraspanins (TSPNs) on the Exo surface. Exos are rich in various TSPNs but predominantly contain CD9, CD63 and CD81. These TSPNs are frequently used to define the presence of Exos, but other studies and our recent preliminary data have shown that Exos can contain highly variable amounts of each TSPN. Our preliminary data suggests that Exos from a glioblastoma cell line contain much less CD81 than Exos from other cell lines, and CD81 is frequently silenced in glioblastoma patients. Therefore, TSPNs may define functional Exo subpopulations. We are using novel mouse models of orthotopically-implanted glioblastoma cells with modified TSPN expression to begin addressing our hypothesis. Exosomes from glioblastoma cells and implants them to nude mice, then we silenced CD9 and CD81 in the same cells and implanted them to nude mice. Results: We have found that overexpression of these tetraspans decreases the survival of tumor bearing mice, and silencing the tetraspans increases the survival of tumor bearing mice.
ABSTRACTS

99 Poster Session A
MicroRNA miR-34c function in tumorigenesis and metastasis of osteosarcoma Huan-Chang Zeng, Baylor College of Medicine; Y. Bae; B. Dawson; E. Munivez; L. Wang; L. Kurenbekova; J. Yustein; F. Gannon; B. Lee

Introduction: MiR-34 is a family of tumor suppressive miRNAs, which is directly regulated by p53 in response to DNA damage and oncogenic stress. In osteosarcoma (OS), expression of miR-34c was decreased as observed in other types of cancer. In our previous study, osteoblast-specific gain of function (GOF) miR-34c mice (Col1a1 2.3 kb-miR34c) showed a critical role of miR-34c in bone homeostasis by regulating Notch signaling. We also found that pathological gain of Notch in committed osteoblastic cells can proliferate immature osteoblasts leading to spontaneous OS. Furthermore, Notch signaling was upregulated in human OS samples. Methods: Tumor suppressive role of miR-34c was assessed by monitoring tumor formation and progression by crossing Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice with Col1a1 2.3 kb-miR34c mice. Results: We performed an experiment to examine the effect of miR-34c on metastasis. Also, tumor reporter murine OS cell lines and syngeneic mouse model (C3H) were used. We assessed the expression of putative miR-34c targets in different OS cell lines. Result: miR-34c was highly expressed in colon cancer mice showed increased survival compared to Col1a1 2.3 kb Ccr+/−: p53 −/− with a trend of less incidence of lung metastasis. We also found miR-34c is significantly decreased in highly metastatic 143B cells compared to other OS cell lines. Furthermore, xenograft studies using 143B-34c (stably expressing miR-34c) showed regression of tumor growth. Based on transcriptome and bioinformatics analysis, we identified several potential targets of miR-34c in OS metastasis. CD2AP and TLK1 are relatively highly expressed in 143B cells compared to non-metastatic cells. The transcript level of these targets was significantly decreased by overexpression of miR-34c mimic in 143B cells. Recently, we have developed Luc reporter murine metastatic OS cell line (Dunn-Luc and LM8-Luc) and assessed tumorigenesis and metastasis property of this cell line using immunocompetent C3H mice. This in vivo mouse model will help us to understand the functional interaction of miR-34c and these targets in lung metastasis. Conclusions: Our study suggests that miR-34c plays a suppressive role in OS and also inhibits metastasis by regulating multiple targets. The molecular function of the inhibitory role of miR-34c in OS metastasis via targeting CD2AP and TLK1 is under way.

100 Poster Session B
Optimizing RNA Biosynthetic Tagging Through Selective Genome Editing Sarah Almasi, The University of Texas Health Science Center at San Antonio; X. Yu; Y. Zhang; A. Pertsemlidis

Introduction: Uracil phosphoribosyltransferase (UPRT) is a pyrimidine salvage pathway enzyme that converts uracil to uridine monophosphate (UMP). Introducing this enzyme into mammalian cells allows them to biosynthesize RNA when grown in the presence of 4-thiouracil (4TU). 4TU is converted to 4-thiouridine monophosphate (4UMP) and then incorporated into RNA. Since mammalian cells do not exhibit UPRT activity and nucleic acids do not innately contain thio-substituted nucleotides, this method allows for cell-specific expression of UPRT. As efficiency of 4UMP incorporation into RNA is critical to the success of such labeling, we aim to eliminate other pathways capable of yielding UMP, directly or indirectly. Uridine monophosphate synthetase (UMPS), which produces UTP, is a thio-substituted uracil synthetase and is the most common and aggressive malignant tumor of the central nervous system with high recurrence and mortality rate. Over the past two decades, the majority of brain tumor drugs entering clinical trial evaluation failed, highlighting the need of finding new therapeutic targets. Recent research identified subpopulations of astrocytes, the mouse equivalent of human glioblastoma cells, that express distinct cellular, molecular, and functional properties. We hypothesize that mouse glioma samples expressing specific astrocyte subpopulation markers can be used for studying subtypes of human glioma. Furthermore, evidences have shown that long non-coding RNAs (lncRNAs) can regulate oncogenes and tumor suppressor genes affecting the proliferation, apoptosis, invasion, migration, and metastasis of tumor cells. Therefore, by investigating lncRNAs with disrupted gene expression in both human and mouse glioma, we can find conserved regulatory mechanisms representing potential therapeutic targets. Methods: We performed a comparative analysis of transcriptomic analysis of reduced cancer cells; the HECT family E3 ligase NEDD4 regulates HER3 signaling and is a biomarker for efficacies of anti-HER3 antibody therapies; and Parkinson Protein 7 (PARK7/DJ-1) association with HER3 expression in both cancer cells and xenograft tumor models. Results: We have found that GOF miR-34c were used. We assessed the expression of putative miR-34c targets in lung metastasis. Results: We found that GOF miR-34c were used. We assessed the expression of putative miR-34c targets in lung metastasis. Conclusions: Based on this, LINC00052-ectopic, or control constructs in nude mice. Results: Profiling analysis showed that LINC00052 expression level changed significantly in response to HER3 knockdown. Gene silencing of LINC00052 diminished both LINC00052 and HER3 expression and reduced cancer cell growth in vitro and in vivo. LINC00052 overexpression promoted cancer cell growth in vitro and in vivo and increased HER3-mediated downstream signaling. Importantly, neutralization of HER3 signaling with HER3 targeting monoclonal antibodies (mAbs) blocked LINC00052 mediated cancer cell proliferation in vitro and tumor growth in vivo. LINC00052 promotes cancer growth through HER3 signaling. Conclusions: Taken together, our results indicate that high LINC00052 levels predict activation of HER3-mediated signaling, and LINC00052 expression level may serve as a potential biomarker for HER3 targeted antibody cancer therapies.

102 Poster Session B
The systematic analysis of protein-coding and long non-coding RNAs in diverse astrocyte populations and their correlates in glioma Raquel Cuevas Diaz Duran, The University of Texas Health Science Center at Houston; Y. You; X. Dong; B. Deneen; J. West

Introduction: Glioma is the most common and aggressive malignant tumor of the central nervous system with high recurrence and mortality rate. Over the past two decades, the majority of brain tumor drugs entering clinical trial evaluation failed, highlighting the need of finding new therapeutic targets. Recent research identified subpopulations of astrocytes, the mouse equivalent of human glioblastoma cells, that express distinct cellular, molecular, and functional properties. We hypothesize that mouse glioma samples expressing specific astrocyte subpopulation markers can be used for studying subtypes of human glioma. Furthermore, evidences have shown that long non-coding RNAs (lncRNAs) can regulate oncogenes and tumor suppressor genes affecting the proliferation, apoptosis, invasion, migration, and metastasis of tumor cells. Therefore, by investigating lncRNAs with disrupted gene expression in both human and mouse glioma, we can find conserved regulatory mechanisms representing potential therapeutic targets. Methods: We performed a comparative analysis of transcriptomic analysis of reduced cancer cells; the HECT family E3 ligase NEDD4 regulates HER3 signaling and is a biomarker for efficacies of anti-HER3 antibody therapies; and Parkinson Protein 7 (PARK7/DJ-1) association with HER3 expression in both cancer cells and xenograft tumor models. Results: We have found that GOF miR-34c were used. We assessed the expression of putative miR-34c targets in lung metastasis. Conclusions: Based on this, LINC00052-ectopic, or control constructs in nude mice. Results: Profiling analysis showed that LINC00052 expression level changed significantly in response to HER3 knockdown. Gene silencing of LINC00052 diminished both LINC00052 and HER3 expression and reduced cancer cell growth in vitro and in vivo. LINC00052 overexpression promoted cancer cell growth in vitro and in vivo and increased HER3-mediated downstream signaling. Importantly, neutralization of HER3 signaling with HER3 targeting monoclonal antibodies (mAbs) blocked LINC00052 mediated cancer cell proliferation in vitro and tumor growth in vivo. LINC00052 promotes cancer growth through HER3 signaling. Conclusions: Taken together, our results indicate that high LINC00052 levels predict activation of HER3-mediated signaling, and LINC00052 expression level may serve as a potential biomarker for HER3 targeted antibody cancer therapies.

Cancer Biology
expressing specific astrocyte subpopulation markers in homologous genomic regions. To understand the possible cis-regulatory functions of homologous differentially expressed IncRNAs, we implemented a systematic correlation analysis of IncRNAs and their neighboring protein-coding genes. **Results:** We found protein-coding genes and IncRNAs with aberrant expression in the different subtypes of human glioma samples. Interestingly, many of the differentially expressed genes in mouse glioma samples have been shown to be highly conserved in homologous regions with altered gene expression in human glioma samples. We found some differentially expressed IncRNAs highly correlated with the expression of protein-coding genes in the close vicinity, similar to their human homologs, indicating possible conserved regulatory mechanisms in cis. **Conclusions:** Different subtypes of glioma may arise from specific subpopulations of astrocytes. Our results demonstrate that RNA-seq data from glioma mouse samples bearing astrocyte subpopulation markers may be used to find potential biomarkers for glioma grade and subtype classification. We are generating a catalogue of differentially expressed IncRNAs with human homologs that are potentially involved in the regulation of glioma. These IncRNAs may represent a novel class of therapeutic targets.

**103**

**Poster Session A**

**NPSD4: a new player in the DNA damage response.** Erin Atkinson, The University of Texas M.D. Anderson Cancer Center; B. Wang

**Introduction:** The DNA damage response (DDR) refers to the mechanisms that are activated upon DNA damage to ensure that DNA is repaired correctly. Improper repair can lead to mutations, oncogene activation, and genomic instability. The DDR involves a series of signaling cascades, potentially regulated by many different types of post-translational modifications, including SUMOylation. Through protein-protein interaction analysis of proteins involved in DDR SUMOylation, we have identified an uncharacterized protein that is recruited to sites of DNA damage that we have named New Player in SUMO dependent DNA damage repair 4 (NPSD4). NPSD4 is recruited to DNA damage tracts and has two SUMO interaction motifs (SIMs), making it a candidate SUMO-regulated DDR protein. Additionally, NPSD4 localizes to the heavily SUMOylated promyelocytic leukemia nuclear bodies (PML NBs) in a SIM-dependent manner. In telomerase negative cancers, PML NBs contain telomeric DNA and are thought to be home to specific telomere recombination complexes. We also examined the telomere maintenance mechanism termed Alternative Lengthening of Telomeres (ALT). We hypothesize that NPSD4 functions in SUMO regulated DNA repair, replication and ALT telomere maintenance.

**Methods:** We performed GST pulldown assays, mass spectrometry, and immunoprecipitation to identify NPSD4 interacting partners. We created point mutations in the SIMs to abrogate SUMO interaction. We used live cell imaging to analyze NPSD4 recruitment to DNA damage sites and NPSD4 localization was evaluated by Immunofluorescence. We generated NPSD4 knockdown cells and performed a DNA fiber assay to evaluate the effect of NPSD4 on DNA recombination. Next, we used SIM DIscovery technology to identify NPSD4 interacting partners. The SIM DIscovery tool analyzes by metaphase spread. ALT activity in NPSD4 knockdown cells was analyzed by c-circle assay. **Results:** NPSD4 preferentially interacts with SUMO2/3 in a SIM dependent manner. NPSD4 forms nuclear foci that colocalize with ALT-associated PML NBs. NPSD4 binds to PML nuclear foci but also forms SIM dependent ALT foci. However, depletion of NPSD4 to DNA damage tracts is not. NPSD4 knockdown cells exhibit a decrease in replication rate and ALT activity. Knockdown of NPSD4 increases sister chromatid exchange. We have confirmed NPSD4 interaction with proteins involved in DDR and replication. **Conclusions:** These results indicate that NPSD4 is likely important for genomic stability and ALT telomere maintenance. As genomic instability contributes heavily to tumor development, characterization of novel DDR proteins can lead to better understanding of tumorigenesis. Additionally, elucidating the ALT mechanism may lead to development of novel therapies for ALT cancers, many of which currently have poor prognoses. Further study is needed to identify the mechanism by which NPSD4 functions.

**104**

**Poster Session B**

**Promyelocytic Leukemia Protein (PML) Supports Mutant KRAS-Driven Lung Cancer.** Smokey Hunt, The University of Texas Southwestern Medical Center; M. Padanad; M. Melegari; J. Rodriquez Canales; I. Wisutha; P. Scaglioni; R. DeBerardinis; J. Minna

**Introduction:** PML, a central component of nuclear bodies (NBs), is a well-established tumor suppressor. However, recent studies revealed that PML supports breast cancer and leukemia progression by modulating lipid metabolism. Depending upon the cellular context, PML can physically associate with different partners in NB and thus regulates different cellular networks, which could explain the paradoxical role of PML In cancer. Activating mutations of proto-oncogene KRAS (mutant KRAS) is associated with aggressive, therapy-resistant non-small cell lung cancer (NSCLC). Since mutant KRAS is still a challenging therapeutic target, there has been an intense clinical interest in identification of downstream player of mutant KRAS. Here, we investigate the role of PML in KRAS driven lung cancer.

**Methods:** To understand the role of PML in mutant KRAS-driven lung cancer, we studied CCSP-rTaTat-K-RasG12D – Pml-/-- mice. To further investigate the role of PML in human NSCLC cell proliferation, we depleted PML was in 16 NSCLC cell lines using shRNAs. Moreover, we used CRISPER/Cas9 technology to knock out PML. To obtain functional and mechanistic data, we used the Seahorse XF-24 Extracellular Flux Analyzer to measure cellular respiration and immunoblot, RT-PCR and mass spectrometry to assess mitochondrial metabolism of NSCLC cell lines depleted of PML. **Results:** We demonstrated that PML is selectively important for cell proliferation in NSCLC cells harboring mutant KRAS but not wild type KRAS. We also found that PML is essential for the ability of mutant KRAS driven NSCLC cells to form colonies in soft agar. Knockdown of PML abrogates ATP production and causes a marked increase in reactive oxygen species (ROS) production in NSCLC cell lines as well as in Pml-/- MEFs compared to wild type MEFs. Silencing of PML shows marked induction of AMP-activated protein kinase (AMPK) and AMPK target genes as well as in reduced mitochondrial respiration. Depletion of PML cause down regulation of genes involved mitochondrial metabolism. In addition, in vivo experiment showed reduced tumor burden in KRASG12D - Pml-/-- mice compared to wild type mice. Altogether, our data suggests that loss of PML results in dysfunctional mitochondria which translated into energy crisis and NSCLC growth arrest. **Conclusions:** Our study suggests that PML cooperates with mutant KRAS to support the rapidly proliferating lung cancer cells via metabolic reprogramming. Taken together our data support a conclusion that PML is involved in metabolic reprogramming and proliferation of lung cancer cells which could provide a potential therapeutic strategy for targeting KRAS driven lung cancer.
to track HNF4α-positive HCC growth with or without manipulation of the Bmal1 protein. Results: These data reveal that HNF4α, generally thought to have tumor suppressor activities, is heterogenous in ALL models. CERS6 knockdown in HCC, where it competes for expression with the core circadian protein Bmal1. HNF4α provides isoform-specific circadian restraint at target cyclin and EMT-related genes. The P2 isoform of HNF4α is unique to HCC cells and downregulates Bmal1. The data reveal that the P2 isoform of HNF4α is primarily involved in the inhibition of direct transcriptional repression of the Bmal1 gene. Forced expression of Bmal1 in HNF4α-positive HCC inhibits viabiliy and migration as well as the growth and progression of tumors in vivo. Conclusions: This study provides the first evidence that the circadian clock is downregulated at the level of Bmal1 by a specific HNF4α nuclear receptor isoform in the context of HCC and that forcing tumors to re-introduce Bmal1 expression results in cell death. These data suggest that targeting the circadian clock by upregulation of the proximal, Bmal1 in HNF4α-positive tumors may provide a new way to inhibit tumor progression.

107 The Chicken Egg Chorioallantoic Membrane Model: A Swiss army knife for generating PDX, deriving vascularized 3D tumors, and developing novel bioassays

Poster Session A

Abstract: The chick chorioallantoic membrane (CAM) model is a highly vascularized extra-embryonic membrane connected to the embryo through a continuous circulatory system, and easily accessible for experimental manipulation. It has been widely used to study angiogenesis and provide a useful model to support the development of biological processes. We have developed various biologically relevant models including Patient Derived Xenografts (PDX), 3D vascularized tumors from cell lines and bioassays for metastasis and radiosensitivity using a novel CAM-based platform technology. Methods: PDX and 3-D Tumors: Patient tumors and cancer cell lines are grafted on the chorioallantoic membrane (CAM) of 5-7 day SPF certified fertilized chicken eggs (white longhorn) along with optimized grafting matrix comprised of laminin, collagen, entactin, and a mix of growth factors. Tumors are allowed to grow for 7-10 days before being harvested. Bone Metastasis Assay: 3-D organoids comprising prostate cancer cells/human adult mesenchymal stem cells (VCApMSC) cells were co-implanted with humanized bovine bone chips onto the CAM, to track the metastatic potential of the prostate cancer cells. Metastatic colonization was confirmed with hematoxylin and eosin (H&E) staining and IHC. Results: We have established 103 CAM-PDX lines from 34 patients across 7 different cancer types with an average take rate of 75-80%. Additionally, 14 CAM-PDX lines have been derived from previously established primary patient-derived breast cancer PDX lines maintained in immunodeficient mice, and from cryopreserved tumor specimens. Our CAM-based platform can also derive highly vascularized 3-D tumors recapitulating the phenotypic hallmarks of the original tumors from multiple cancer cell lines including breast, prostate and colorectal. Using the CAM-based platform we have successfully modeled the interactions between reactive endosteam on trabecular bone and metastatic cancer cells. This novel system allows us to demonstrate the ability of Tenasin-C coated trabecular bone clefts to recruit CAM blood vessels in order to colonize VCAp cells. The system can be extended to other cancer types to study mechanisms of metastasis. A major advantage of our model is the easy access to the tumor graft/plaque, which can be exploited to administer various drugs/anti-cancer compounds and make real-time assessments of tumor response using imaging methods like MRI and IVIS. Conclusions: In conclusion, we have developed a rapid, scalable, and cost-efficient novel chicken egg-based platform technology with a potential to accelerate cancer research and discovery.

108 Ceramic Synthase-6 alters sensitivity of Acute Lymphoblastic Leukemia cells to ABT-737, a pan-BCL-2 family of Protein inhibitor and Dexamethasone

Poster Session B

Abstract: Ceramic synthase-6 (CERS6) is one of the enzymes that synthesize complex sphingolipids, are synthesized by the enzyme ceramic synthase (CERS). Six different isoforms of ceramic synthase (CERS1-5, CERS6) with varying substrate specificity generate ceramides of diverse chain length and acyl group. CerS6 plays a role in regulation of cell cycle, differentiation, apoptosis and senescence. In normal tissues, CERS2, an enzyme synthesizing ceramides with C24 acyl chain (C24,C)-Cer, is highly expressed and has the widest tissue distribution while CerS6 generates C16-Cer with low and tissue-specific distribution. Our preliminary data showed that CERS6 levels were significantly higher in acute lymphoblastic leukemia (ALL) cells in comparison to Peripheral Blood monoclonal cells and T-Lymphocytes derived from healthy human volunteers. The purpose of this study is to investigate the role of CERS6 in chemoresistance and metastasis. Herein, we showed that CERS6-C16-Cer levels were significantly higher in acute lymphoblastic leukemia (ALL) models in comparison to different cell lines. In a viability test performed with Annexin-V using flow cytometry. Stable overexpression and knockdown of CERS6 was achieved by lentiviral vector system. Statistical comparison of the results was carried out using unpaired student’s t-test with Welch’s correction. Cytotoxicity of conventional and investigational anti-leukemia agents was evaluated in T-cell ALL cell lines with CERS6 knocked-down and overexpressed. Results: CERS6 knockdown significantly decreased C24-Cer by four-fold (p<0.01) while CERS6 overexpression increased C24-Cer by two-fold (p<0.05). CERS6 knockdown in CCRF-CEM cells increased their sensitivity to a pan-BCL-2 inhibitor ABT-737 as well as glucocorticoid (dexamethasone). The percent survival at 72h in ABT-737 (100nM) or dexamethasone (100nM) for 72h was 39% (p<0.001) and 40% (p<0.001) relative to 2% and 1% for vector control. Higher cleaved PARP, cleaved Caspase 3 and cleaved Caspase 8 were observed in CCRF-CEM cells with CERS6 knockdown, which was reversed by overexpression of CERS6, suggesting that CERS6 alters ALL cell sensitivity to anti-leukemia drugs via extrinsic pathway of apoptosis. Conclusions: This study revealed CERS6 expression was inversely affected the sensitivity to ABT-737 and dexamethasone in ALL cell lines via extrinsic apoptotic pathway. Understanding the mechanism by which CERS6 interferes with apoptosis, could enable discovery of novel targets for ALL treatment.

109 LinkerMedics: analyzing multi-omics data within and across 32 cancer types

Poster Session A

Abstract: The Cancer Genome Atlas (TCGA) project has performed massive molecular profiling of human tumors using genomic, epigenomic, transcriptomic, and proteomic platforms, and each tumor is comprehensively characterized by around 100,000 molecular attributes in addition to typical clinical attributes. To make these data directly available to the entire cancer research community, several data portals have been developed. However, none of the existing data portals allow systematic exploration and interpretation of the complex relationships between the vast amount of clinical and molecular attributes. Methods: We developed LinkerMedics (http://www.linkermedics.org), a web platform that focuses on the discovery and interpretation of associations between clinical and molecular attributes. LinkerMedics includes three data analysis modules. The LinkFinder module allows flexible exploration of associations between a molecular or clinical attribute of interest and all other attributes, providing the opportunity to analyze and visualize associations between billions of attribute pairs for each cancer cohort. The LinkCompare module enables easy visualization of the common patterns identified by the LinkFinder, which is particularly useful in multi-omics and pan-cancer analyses. The LinkInterpreter module transforms identified associations into biological understanding through the pathway and network analysis. All modules provide user-friendly data visualization. Results: The current version of LinkerMedics contains multi-omics data and clinical data for 32 cancer types and a total of 11,158 patients from the TCGA project. It is also the first multi-omics database that integrates mass spectrometry (MS)-based global proteomics data generated by the Clinical Proteome Tumor Analysis Consortium (CPTAC) on 32 tumor samples. In total, LinkerMedics has more than a billion data points. We used several case studies to demonstrate the utility of LinkerMedics in revealing functional impact of somatic mutation or copy number alteration on mRNA or protein expression, in deriving multi-omics based protein signatures for poor prognosis, in performing pan-cancer analysis to identify survival-associated gene expression signature, and in connecting novel pan-cancer poor prognosis markers to tumor invasiveness and aggressiveness. Conclusions: LinkerMedics provides a unique platform for biologists and clinicians to access, analyze and compare cancer multi-omics data within and across tumor types.

110 Cyclic Mechanical Strain Regulates Cancer Drug Resistance and Metastatic Potential

Poster Session B

Abstract: Drug resistance and metastasis are two major barriers to the effective treatment of cancer. A major limitation in the discovery and development of drugs that overcome drug resistance or prevent the
spread of cancer is a lack of high throughput in vitro assays that accurately recreate the cell-cell interactions and mechanical forces that occur during cancer progression and metastasis. Moreover, using cancer patient-derived cell lines, cyclical mechanical strain in the regulation of drug resistance, we used a high throughput biaxial oscillating stretch system (HT-BOSS) to mechanically strain cancer cells at a range of percent strains. Cells were plated in custom-made well plates with flexible silicone membrane bottoms. MDA-MB-231 breast cancer cells were mechanically strained for 24 hours at strains ranging from 0 – 17.5% strain. RNA sequencing, immunostaining, cell adhesion, and drug resistance studies were conducted to assess drug resistance and metastatic potential after cells were conditioned with mechanical strain. Cancer cell adhesion to endothelial cells in the presence of high fluid flow was used as one metric to evaluate metastatic potential in cells. Breast cancer cells were conditioned with mechanical strain at a range of strains and then an adhesion assay was performed in the presence of shear stress. Results: Conditioning with mechanical strain resulted in a decrease in proliferation of MDA-MB-231 breast cancer cells compared to control cells. We determined the clinical relevance, we also analyzed the expression levels in breast cancer cells and assessed the impact of NELF expression, gene expression, protein expression, and functional assays.

111 Poster Session A
NELF-mediated RNA polymerase II pausing contributes to BRCA1-associated breast cancer development and progression
Chi Zhang, The University of Texas Health Science Center at San Antonio; L. Zhou; B. Yang; R. Li
Introduction: Negative elongation factor (NELF), a four-subunit protein complex (NELFA, B, C/D and E), is well known for its function in mediating RNA polymerase II pausing at the promoter-proximal region. Published work indicates that NELF plays physiological roles in tissue development and homeostasis. Notably, recently published work from our laboratory demonstrates that tissue-specific deletion of NELFB in mouse mammary gland results in severely development defects. However, the role of NELF in cancer development and progression remains unclear. Previous study of our lab found that NELFB/COBRA1 directly interacts with BRCA1, thus offering a potential link between NELF and the tumor-suppressing activity of BRCA1. Hypothesis: In this study, we explored the role of NELF’s function in the initiation of BRCA1-associated breast cancer, we generated mammary epithelium-specific BRCA1 and COBRA1 double knockout mice. We compared normal mammary development and tumor development between BRCA1/NELF single and double knockout mice. To study gene changes in the L1T2 cell line, cells were treated for 4 weeks with protease Inhibitors and/or nelfinavir treatment and changes were measured in the L1T2 cell line.

Results: Results showed taxol treatment led to higher expression of ABCG2, as well as ABCB1, in the L1T2 cell line, cells were treated for 4 weeks with protease inhibitors, and examined gene expression changes. To study gene changes in the L1T2 cell line, cells were treated for 4 weeks with protease inhibitors and/or taxol after which RNA was isolated and gene expression was measured with a custom TaqMan low-density array (TLDA). To determine whether L1T2 cells express functional P-gp, first cell membrane expression was measured by flow cytometry in untreated L1T2 cells and treated cells, then efflux of the fluorescent substrate rhodamine 123, and three-day cytotoxicity assays were performed on L1T2 cells or L1T2 treated cells. Results: Results showed taxol treatment led to higher expression of ABCG2, as well as ABCB1, in the L1T2 cell line. Meanwhile, treatment of breast cancer cells with integrin inhibitors while cells appear to be significantly less proliferative while being strained. Mechanical strain at strains ranging from 2.5 – 17.5% increased adhesion of breast cancer cells to endothelial cells in the presence of fluid flow. Mechanical strain decreased the expression of drug resistance genes and increased the expression of drug sensitive genes. These two steps, resulting in multi-drug resistance in cancer cells, were attenuated by mechanical strain. Conclusions: Our findings indicate that cyclic mechanical strain regulates drug resistance, proliferation, and cell adhesion in the presence of fluid flow in MDA-MB-231 breast cancer cells as demonstrated through gene expression, protein expression, and functional assays.
develop secondary lesions have a 20% survival rate. Because current treatments are not as beneficial to patients with metastatic disease, our project is focused on understanding genes which enhance primary lesions ability to adopt a more aggressive behavior. Our institute and other research groups have shown that patients with 8q24 amplification have a worse prognosis compared to those who have chromosomal balance of this same region. Besides c-Myc, this region harbors a long non-protein coding RNA called plasmacytoma variant translocation 1 (PVT-1). The aim of our study is to characterize the phenotypic and mechanistic role of PVT-1 in osteosarcoma. **Methods:** The phenotypic role of PVT-1 is done by using an osteosarcoma cell line, HOS, which has either stable overexpression of PVT-1 or the corresponding blank control. We used these cell lines to perform proliferation, migration, and invasion assays. In addition, In Vivo studies are currently being conducted to identify if the In Vitro results could be recapitated in a whole organism. Secondly, we will elucidate the mechanism which PVT-1 uses to promote these tumorigenic behaviors. The mechanism(s) will be identified by determining PVT-1 direct binding partners and this will be done by using Chromatin Isolation by RNA Purification followed by mass spectrometry/sequencing. To determine potential signaling pathways dependent or downstream of PVT-1, we will perform Reverse Phase Protein Array and Gene Expression Array. Subsequently we will perform In Vitro and In Vivo studies to verify the existence of these pathways. **Results:** PVT-1 is overexpressed in a significant subset of human osteosarcoma sample tumors. In Vitro studies demonstrate that overexpression of PVT-1 enhances proliferation, migration, and invasion phenotypes. In addition, In Vivo experiments use fo 5 different cell lines. Conclusively, we will perform Reverse Phase Protein Array and Gene Expression Array. Subsequently we will perform In Vitro and In Vivo studies to verify the existence of these pathways. To determine potential signaling pathways dependent or downstream of PVT-1, we will perform Reverse Phase Protein Array and Gene Expression Array. Subsequently we will perform In Vitro and In Vivo studies to verify the existence of these pathways. Second, we will elucidate the mechanism which PVT-1 uses to promote these tumorigenic behaviors. The mechanism(s) will be identified by determining PVT-1 direct binding partners and this will be done by using Chromatin Isolation by RNA Purification followed by mass spectrometry/sequencing. To determine potential signaling pathways dependent or downstream of PVT-1, we will perform Reverse Phase Protein Array and Gene Expression Array. Subsequently we will perform In Vitro and In Vivo studies to verify the existence of these pathways. **Conclusions:** PVT-1 is a potent oncogene in osteosarcoma and plays an important role in driving aggressive behavior.
which neutrophil elastase contributes to metastasis could lead to novel therapeutic interventions for treatment of metastatic breast cancer.

Methods: Flow cytometry was used to evaluate immune cell populations in organs and tumors. Multiplex assays were used to measure serum cytokines. FACS was used to purify cell subsets from tumors and RNA expression was assessed by qRT-PCR. Mice: FVB/N-Tg(MMTV-PyMT)634Mul/J; B6.129X1-Elane<sup>−/−</sup>; C57BL6/J Cell lines: Polyclonal PyMT tumor cell line derived from PyMT + C57BL6/J mouse, acquired from DG DeNardo (Department of Pathology & Immunology, Washington University School of Medicine in St. Louis). Results: PyMT tumors drove the expansion and mobilization of myeloid populations from the bone marrow. Deletion of neutrophil elastase had no effect on the development or distribution of neutrophils in steady state conditions; however, in PyMT+ tumor-bearing mice, removal of neutrophil elastase reduced the frequency of specific myeloid populations, including neutrophils and macrophages, in the lungs and liver. Serum cytokine analyses revealed that PyMT+ mice lacking neutrophil elastase had reduced levels of G-CSF, CCL2, CCL7 and CXCL1, compared to tumor bearing mice with neutrophil elastase. In mice orthotopically injected with a PyMT tumor cell line, tumor volume was reduced two-fold in mice without neutrophil elastase. RNA expression analyses of purified populations isolated from the tumor microenvironment revealed that PyMT tumor cells and the non-immune stroma produced G-CSF. In contrast, CCL2, CCL7 and CXCL1 were produced by the immune infiltrate within the tumors. Conclusions: Neutrophil elastase promotes tumor growth and is correlated with increased levels of myeloid growth factors and chemoattractants that can be produced in the tumor microenvironment. Elevated expression of these factors may influence the abundance and infiltration of myeloid populations in the lungs and other organs of tumor-bearing mice. Future studies will determine the specific roles of neutrophil elastase in promoting these immune populations and how they contribute to tumor growth and metastasis.

Kinetics of small molecule interactions with membrane proteins in single cells measured with mechanical amplification

Yan Guan, Arizona State University

Introduction: Advances in structural biology have led to an exponential growth in the number of membrane proteins with the determined three-dimensional (3D) structures. However, to understand the cellular functions of membrane proteins, it is also necessary to determine the interaction kinetics of the membrane proteins with various molecules. This is because cells perform many functions, including communication, through the interactions of their membrane proteins with molecules in the extracellular medium. However, measuring the interactions of molecules with membrane proteins in the natural lipid environment has been a difficult task. Methods: The mechanical deformation is expected because the law of thermodynamics predicts that when molecules bind to a surface, the surface tension changes, leading to a mechanical response in the cell membrane. According to thermodynamics, the surface concentration of molecules bound on the membrane surface is proportional to the derivative of surface tension and to the chemical potential of the molecules. At the same time, the chemical potential is related to the bulk concentration. Therefore, the molecular binding is directly proportional to the surface tension change, and thus, the molecular interactions with the membrane proteins can be determined by measuring the mechanical deformation in the membrane. Results: We report an observation of mechanical deformation of cells upon interactions of the cellular membrane proteins with molecules in the extracellular medium, and demonstrate a real-time analysis of the interactions in single cells by analyzing the mechanical deformation with subnanometer resolution. Our measurement is based on a differential detection method that provides subnanometer accuracy to monitor cell edge deformation. Using this capability, we have monitored the kinetics of both large and small molecule interactions with membrane proteins, including glycoproteins and ion channels in intact cells (fixed or living), and obtained the binding kinetic constants. For large molecules, the kinetic constants agree with those obtained with a plasmonic imaging technique. For small molecules, the present method represents the first kinetic measurement, and direct comparison with other techniques is not possible, but the equilibrium constants extracted from the present method are consistent with those obtained with end-point radioactive labeling assays. The imaging capability allowed us to reveal cell-to-cell variability and region-to-region variability within the same cell. Conclusions: This new strategy provides mechanical amplification of small binding signals, making it possible to detect small molecule interactions with membrane proteins. This capability, together with spatial resolution, also allows the study of the heterogeneous nature of cells by analyzing the interaction kinetics variability between different cells and between different regions of a single cell.
Poster Session B

DNA Compatible Nitro Reduction and Benzimidazole Synthesis

Huang-Chi Du, Baylor College of Medicine; H. Huang

Introduction: DNA-encoded library (DEL) has emerged as a cost-effective platform for hit generation. The chemical and structural diversity of small molecules displayed by the DEL, and are compatible with structurally diverse building blocks is key to the preparation of productive DNA libraries. However, this is limited by the availability of efficient synthetic methods that enable facile derivatization of both acids and amines. DNA-conjugated sterically hindered carboxylic acids. The reactions were optimized by systematically changing various parameters (temperature, buffers, pH and concentration) and the optimized conditions were then applied to a wide range of acids and amines. DEL synthesis compatibility was also investigated using DNA tag ligation. In addition, the mechanism of activation of acid in water was also investigated by PyAop stability tests. Results: The PyAop mediated acylation was optimized by temperature, buffer media and the sequence of adding reagents. The reaction offered a broad substrate scope in terms of both acids and amines. DNA-conjugated stericly hindered carboxylic acids efficiently coupled with a wide variety of amines. Successful DNA tag ligation showed that the PyAop mediated acylation is compatible with structural modification. Conclusions: Facile and versatile PyAop mediated coupling between DNA-conjugated carboxylic acids and amines in aqueous media was successfully developed. The new protocol demonstrated a broad substrate scope. The reaction conditions were compatible with the DNA structure and were amenable to DEL synthesis.

Poster Session B

Cryo-EM structural refinement of cancer targets at near-atomic resolution

Fengyun Ni, Baylor College of Medicine; T. Ma; Z. Tang; J. Mic; Q. Wang

Introduction: Cryo-electron microscopy (Cryo-EM) has emerged as a promising technique for understanding molecular mechanisms of carcinogenesis and progression. Hardware advances in recent years have allowed atomic-resolution single-particle Cryo-EM reconstruction for macromolecular assemblies with high symmetry. However, this atomic resolution is still beyond the reach for many biomolecular assemblies of lower or no symmetry. Thus, there is an urgent need for advanced computational methods to aid in Cryo-EM reconstruction at near-atomic resolution. Our lab recently developed a powerful Parallel Continuous Simulated Tempering (PCST) algorithm that is highly efficient in accelerating barrier crossing and finding native structures than a conventional simulated annealing method. In this study, we introduce the PCST algorithm to refine Cryo-EM structures of three cancer targets at near-atomic resolution. Methods: To benchmark the applicability of PCST algorithm to Cryo-EM structural refinement, we chose common cancer targets: 2OS proteasome (6.8 Å), AAA ATPase p97 (6.9 Å), and group II chaperonin Mm-cpn (8.0 Å). The initial model will be used to prepare a structural-based force field to guide conformational search by PCST algorithm. Plausible models are selected from resulting trajectory by statistical assessment, and then feed into Cryo-EM density map. Conclusions: The models will be further analyzed in three aspects: 1) to examine the model quality by calculating geometry statistics; 2) to convert root mean square fluctuation of the system to atomic B-factors that will be compared with resolution distribution of experimental map; and 3) to identify the potential functional motions of the system through structural ensemble analysis of the trajectory. Results: By examining the quality of refined structures from our studies and comparing with corresponding high-resolution crystal structures if available, these test cases will demonstrate the applicability of PCST algorithm to Cryo-EM structural refinement at near-atomic resolution. The enhanced sampling efficiency of PCST algorithm generates better conformations for fitting into Cryo-EM map. Investigating long-term structural fluctuations of a structural model will provide a more valid description of Cryo-EM map quality. Structural ensemble analysis of the PCST trajectory will shed new light on dynamic properties intrinsic to a given system. Conclusions: With the combination of structural-based modeling and enhanced sampling by PCST, our strategy not only improves Cryo-EM structures at near-atomic resolution, but also better interprets experimental map quality. This method is expected to help solve Cryo-EM structure of Polycomb repressive complex 2, a master epigenetic regulator.
Enantioselective Synthesis of CIDD-0072424; A PKC epsilon Inhibitor to Reduce Alcohol and Nicotine Consumption for Cancer Prevention
Hua-Yu Wang, The University of Texas at San Antonio; R. Messing; J. Wang; S. McHardy

Introduction: One-fifth of the world’s population uses tobacco products, and in the US approximately 50% of all cancer deaths are attributable to smoking. Tobacco use increases risk of cancer of the lung, mouth, larynx, pharynx, esophagus, stomach, colon, rectum, liver, pancreas, kidney, and possibly breast, and of myeloid and lymphoid leukemia. Almost 40% of the world’s population consumes alcoholic beverages and 15% of adults and teenagers over 15 years of age engage in binge drinking, with women accounting for the majority of the increase in binge drinking since 1998. The lifetime use of alcohol for adults in the US has remained fairly stable, with approximately 15% of adults and teenagers engaging in binge drinking. In the same timeframe, the number of cigarettes smoked per adult per day in the US has decreased by approximately 30%. Therefore, there is considerable need for the development of new therapeutic agents to treat these disorders. Current evidence indicates that protein kinase C epsilon (PKCe) is a good target for development of drugs to treat alcohol and nicotine use disorders, based partially on studies using gene-targeted mice that lack this enzyme (Prkce-/- mice). Preliminary animal studies also show PKCe inhibitors provide robust activity in ethanol and nicotine addiction models, as well as various pain models. Through a collaboration with the UT Austin Waggoner Center, the goal of our work is to develop new, selective, and highly effective PKCe drugs to treat alcohol and nicotine use disorders. Methods: With good CNS active lead PKCe inhibitors identified, there was a major unmet research need to improve the current synthesis of these lead compounds and provide a robust synthesis route that is enantioselective, scalable and efficient in order to easily access the structural diversity for 3-point structure-activity relationship (SAR) studies. To this end, we utilized an asymmetric Nitro-Mannich reaction as the key step in building the desired chiral diamine moiety present in lead PKCe compounds. Results: After screening several organocatalysts and conditions, the key Nitro-Mannich reaction sequence was achieved in 96% yield with no enantiomeric excess. The overall synthesis provided the desired compound in 8 steps and 35% overall yield. Conclusions: The new and improved enantioselective synthesis of CIDD-0072424 provides the desired compound in high yield and high optical purity, as well as allows for rapid, 3-piont SAR studies. This presentation will highlight the new enantioselective synthesis of CIDD-0072424 and PKCe SAR studies, as well as key ADME data on this lead compound.

Development of an informatics platform for the analysis of DNA-encoded library screens to enable small molecule drug discovery
Kevin Riehle, Baylor College of Medicine; J. Faver

Introduction: DNA-encoded library (DEL) screening is a modern small molecule drug discovery strategy which combines the strengths of combinatorial chemical synthesis and high-throughput DNA sequencing. Such libraries (which typically contain millions to billions of unique molecules) are assayed for binding affinity as a complex mixture, and the identities of potential hit compounds are determined via DNA sequencing. Compared to other drug discovery platforms, successful DEL screening efforts require unique requirements for informatics support which may not be as standardized as methods for high-throughput screening (HTS). To enable DEL screening at Baylor College of Medicine, we have heavily customized our registration environment (Dotmatics software) to allow scientists to manage information about libraries, selection experiments, and sequencing runs in addition to using common features like inventory and electronic lab notebooks (ELNs). Methods: This project is supported by a computational cluster and series of virtual machines (VMs) deployed to manage each aspect of the project. The computational cluster allows for the scheduling of many parallel jobs, which decreases the turnaround time and better optimizes the cluster usage by running a series of jobs that have specific hardware requirements. Sequence output (Illumina MiSeq, NextSeq, and HiSeq) resulting from the DEL screen is uploaded via FTP and data files are subsequently accessible on each server / VM, allowing for seamless access to data from any machine within our customized platform. Uploaded sequence files are then linked to their corresponding experiments, which triggers the automated pipeline to decode the results of the selection by querying the registration system for all necessary input. Results: We have developed a semi-automated informatics pipeline that decodes the results of DEL screens, leveraging the information (library design, experimental conditions, analysis settings, and amplicon structure) stored in our customized registration environment. Conclusions: Customized environments can enable alternative drug discovery platforms via integration with in-house pipelines which provide new functionalities on top of the built-in features (commercially available and open source solutions) to aid in automation and analysis of DEL screens.

Bioinformatics Core Facility at UT Southwestern Medical Center Gaudenz Danuser, The University of Texas Southwestern Medical Center; B. Cantarell; Y. Xie; M. Kim

Introduction: For the past two years we have been building a core facility that serves the cancer community at UT Southwestern in solving bioinformatics tasks. The facility is being established in parallel to the launch of the Lyda Hill Department of Bioinformatics, which grows as an outgrowth of the Lyda Hill Initiative for Training in bioinformatics. Methods: The Bioinformatics Core Facility (BICF) serves the community in two categories: 1) Foundational services include a help desk, which answers bioinformatics-related questions on the spot or triages complex tasks into one of four top-tier services (see below). Foundational services also include nanocourses, which are two-day courses covering theory and practice of bioinformatics methods; and provision of software pipelines and curated databases that give the cancer researcher with limited bioinformatics expertise convenient access to state-of-the-art data analytical tools. 2) Top-tier services include a bioinformaticist-on-demand program, where a project director can hire a BICF staff member to work on a particular project. The value of this program for the campus is that BICF offers a standing pool of bioinformatics talent, which dramatically streamlines recruitment times and retains know-how locally. Results: This program has been attended by 15-20 projects per year, we have accommodated 10 - 15 bioinformaticist-on-demand projects, and we have launched 4 major flagship projects. Most importantly, one of these flagship projects contributed bioinformatics analytics to a CLIA-certified genomomic cancer screening pipeline that is now offered at UT Southwestern. Conclusions: The launch of BICF has fundamentally changed the quality and accessibility of bioinformatics for cancer research and clinical work at UT Southwestern.
hosted a symposium to showcase successful core supported projects. **Conclusions:** We will continue most of the Core projects initiated during the first fund period in subsequent years. Additional new projects are anticipated. We anticipate significant outcomes from some of the projects in the coming years in terms of patent filings, licensing agreements, publications and funded grant proposals.

### 130 CPRIT Grantee Poster Session B

**Collaborating with the Center for Drug Discovery at Baylor College of Medicine Using DNA-Encoded Chemical Libraries Hongbing Huang, Baylor College of Medicine; J. Anglin; M. Bangs; K. Bohren; J. Campbell; S. Chamakun; Y. Chen; M. Chung; M. Corsello; S. Dillard; H. Duv; J. Favier; S. Gudur; P. Jain; Z. Jin; J. Li; G. Miklo; O. Miklossy; C. Mert; N. Nigidi; P. Nyshadham; M. Palaniappan; K. Riehle; P. Rosner; C. Santini; N. Simmons; S. Trivedi; N. Ucicis; Y. Wang; D. Young; Z. Yu; M. Matzuk**

**Introduction:** DNA-encoding chemical libraries (DELs) is a cost-effective alternative technology for hit generation that addresses the limitations and economic shortcomings of high-throughput screening (HTS). DELs are collections of organic compounds in which each structure is tagged with a DNA identification barcode. In analogy to phage-display technology, the DNA-tag facilitates the synthesis and allows the simultaneous screening of very large sets of compounds. The screening process typically involves affinity selection of libraries against a protein target in a single affinity step. The advent of high-throughput, next-generation sequencing technology for high-throughput DNA sequencing allows simultaneous interrogation of hundreds of millions of compounds at a fraction of the cost for conventional HTS. **Methods:** Employing combinatorial chemistry, we have established a novel DNA-encoded Chemistry Technology (DEC-Tec) platform that leverages the encoding power of DNA to create large collections of small molecules for hit identification. DEC-Tec enables the exploration of greater chemical space than is achievable through traditional HTS methods, resulting in the direct discovery of high-affinity ligands to disease targets. **Results:** Applying novel reaction methods and chemistry schemes, we have built diverse DNA-encoded chemical libraries that consist of more than 1.5 billion unique drug-like small molecules. Successful selections have been conducted on a diverse set of protein classes including enzymes, binding proteins and transcriptor factors. High affinity binders have been characterized in biochemical and biophysical assays. We also obtained co-crystal structures of lead compounds bound to target proteins, which will aid structure-based drug design. **Conclusions:** To serve the biomedical research community in Texas, we have established a straightforward process for collaboration. This collaboration approach will expedite the discovery of novel chemical probes and drug candidates for cancer treatment.

### 131 CPRIT Grantee Poster Session B

**North Texas Clinical Pharmacology Cancer Core Troy Putsman, Texas Tech University Health Science Center at Dallas; I. Subramanian**

**Introduction:** The North Texas Clinical Pharmacology Cancer Core (NTCPCC) was established to facilitate translation of basic cancer research into improved care for cancer patients. In order to accomplish this goal, a state-of-the-art analytical/bioanalytical facility was established to help basic cancer researchers and physicians better understand the pharmacoekinetics, pharmacodynamics and metabolism of current and potential cancer therapeutics. **Methods:** Overall, the NTCPCC uses its expertise and advanced instrumentation in collaborations with cancer investigators to design and execute studies to understand (1) the optimal dose and schedule for a variety of therapeutic agents, and (2) the metabolism of the therapeutic. These aspects are studied in order to maximize efficacy and decrease unwanted side effects. **Results:** A discussion of the current instrumentation and capabilities of the NTCPCC will be presented. Additionally, a summary of current projects will be provided. **Conclusions:** The NTCPCC has been successful in establishing a core facility with the expertise and instrumentation to achieve its specific aims. The NTCPCC has also established active collaborations with cancer investigators and has been successful in conducting several clinical pharmacology focused studies. These collaborations and studies demonstrate that the NTCPCC is achieving its overall goal to help facilitate translation of basic cancer research into improved care for cancer patients.

### 132 CPRIT Grantee Poster Session B

**Precision oncology decision support core - a high quality, comprehensive clinical research support system VilaKumar Holla, The University of Texas M.D. Anderson Cancer Center; J. Zeng; A. Bailey; A. Johnson; N. Sanchez; Y. Khotksaya; B. Litenburger; M. Shufan; A. Simpson; M. Routbott; J. Rodon; T. Yap; E. Bernslam; G. Mills; J. Mendelsohn; K. Mills Shaw; F. Merci-Bernstam**

**Introduction:** Cancer is a heterogeneous disease driven by mutations in patient’s germline and somatic DNA. Next-generation sequencing (NGS) offers new paradigms to understand patients based on their tumor genomic profiles. NGS has yielded vast amounts of mutational data, hindering interpretation of the role individual mutations play in tumorigenesis by oncologists without the help of bioinformatic infrastructure. Precision Oncology Decision Support (PODS) core was established to provide point-of-care support locally and across the state of Texas. This includes funded PODS core recent progress. **Methods:** PODS core has continued to develop a computational infrastructure that streamlines the annotation process of variants, drugs, and clinical trials. Genomic alterations, therapeutic agents, and clinical trials were annotated using a combination of manual and built-in literature retrieval tools. The functional significance of each variant was assessed and linked to appropriate targeted agents and clinical trials. Annotations were aggregated in a dynamic fashion to facilitate the generation of patient reports, which included a list of matching clinical trials. **Results:** PODS core has built an oncology-centric knowledgebase that is continuously updated. In addition, we increased the breadth of PODS knowledgebase with annotation of drugs (total of 2,354) and clinical trials (total of 4,468). Consequently, PODS generates patient reports that contain variant actionability along with a customized list of matching clinical trials. In addition, we have also implemented an online portal to allow for annotation request submission. To date, PODS has delivered 3,379 total patient reports, covering 14,071 mutations (6,972 unique), to 169 physicians at MD Anderson. Proactive trial alerts were implemented to alleviate physicians’ need to keep up-to-date on available clinical trials. To date, 204 proactive trial alerts on 31 genes were sent to 169 physicians. Based on these efforts, enrollment on genotype-selected or relevant trial at MD Anderson has been slowly increasing. To capture whether individual reports are acted upon, a clinical decision follow-up questionnaire is sent to all annotation requesters. Finally, many annotations are available via https://pct.mdanderson.org that provides information on 652 functionally or therapeutically significant alterations across 33 genes. **Conclusions:** The development of the PODS core has enhanced the awareness of targeted therapies matched to each patient’s molecular profile, increased accrual to genotype-selected trials. We have begun to explore the collaboration with The University of Texas Southwestern Medical Center (UTSW) to help annotate variants from UTSW patients and generate clinical reports.

### 133 CPRIT Grantee Poster Session B

**Development of a cheminformatics platform for DNA-encoded library screening John Feyer, Baylor College of Medicine; K. Riehle**

**Introduction:** DNA-encoded library (DEL) screening has become a powerful strategy for hit identification in drug discovery by combining the strengths of combinatorial chemistry and next generation DNA sequencing. In this discovery platform, DEL libraries (which typically contain millions to billions of unique molecules) are screened for binding affinity to biological targets as a complex mixture. The identities of potential hit compounds are then determined via DNA sequencing and statistical analysis. Compared to other drug discovery platforms, successful DEL screening has unique requirements for informatics support which are not as standardized as methods for traditional high-throughput screening (HTS). To enable DEL screening at Baylor College of Medicine, we have developed custom software and data pipelines which handle a broad range of activities from simple data entry to automated analysis of large and complex data sets. **Methods:** Our overall informatics infrastructure is built around three key components: a Dotmatics informatics suite, an automated DNA decode pipeline, and a custom cheminformatics server. Both the DNA decode pipeline and the cheminformatics server were developed in-house to provide functionality specific to DEL library screening, and are closely linked to the commercially available Dotmatics informatics system. **Results:** Our in-house cheminformatics server includes DB schemas, query forms, and data visualizations. It is built around three key components: the Dotmatics informatics suite, data pipelines, and electronic laboratory notebooks. We have enhanced the utility of the Vortex data analysis software by developing custom scripts which interact with the in-house cheminformatics server to enable DEL related tasks. **Conclusions:** Custom data pipelines and in-house application servers in combination with standard informatics software can be used to enable alternative drug discovery platforms by providing novel functionalities to supplement those commonly available in commercial informatics suites. This work was supported by the Core Facility Support Award U54P50180085 from the Cancer Prevention Research Institute of Texas (CPRIT).
Introduction: Endometrial cancer is the most common malignancy in the reproductive track. Risk is increased with age, with diagnosis at an average of 60 years, but also obesity-associated endometrial cancer is on the rise in a younger age group (around 40 years). In this project, we tested the hypothesis that disruption of genes controlling cell-cell communication, including gap junction and tight junction genes, referred to here as the communicome, may lead to the development of endometrial cancer lesions. Loss of function and dysregulation by demethylating agents and exposure to altered paracrine environments. Single-cell transcriptomics analysis was used to assess endometrial cell heterogeneity in the endometrium, which may lead to the development of endometrial lesions. Results: DNA methylation of candidate communicome loci involved in regulation of gap junction channel communication was significantly (p<0.01) more prevalent in endometrial tumors from obese and morbidly obese patients. Treatment of endometrial cancer cells with demethylating agents restored gap junction activity and cellular interactions. Adipose stromal cell paracrine actions affected the expression of the communicome gene expression profile, leading to the suppression of key modulators of gap junction activity. On the other hand, peritoneal mesothelial paracrine actions resulted in an enhancement of endometrial cell gap junction communication associated with endometriosis lesions. Motion of the piperazine side chain into the peritoneal mesothelial cell lining, reactivation of intercellular communication may be an essential component for cellular invasiveness.

Conclusions: Epigenetic silencing of intercellular communication may be a factor in endometrial cancer development. On the other hand, during active heterotypic invasive processes such as endometriosis lesion establishment into the peritoneal mesothelial cell lining, reactivation of intercellular communication may be an essential component for cellular invasiveness.

136 Design and production of piperazine-2-acetic acid esters as tools for drug discovery using systematic chemical diversity. Shreya Guduru, Baylor College of Medicine; D. Young; K. MacKenzie; P. Jain; I. Raji; S. Chamakuri; C. Santini

Introduction: The hunt for new drugs to treat cancer generally involves two important steps: 1. The identification and isolation of biochemical targets implicated in the initiation and sustenance of the cancerous condition. 2. Exposure of the target to groups of experimental compounds that can interact with it and produce effects that inhibit or reverse the cancerous process. Design of experimental compounds uses principles formulated by clinical experience. Production of experimental compounds is accomplished using synthetic organic chemistry. Methods: Among the strategies used to design and create compound collections (“libraries”) used for drug discovery, two in particular are being pursued by our laboratories: 1. Fragment Based Ligand Discovery (FBLD) 2. DNA Encoded Compound Technology (DEC-Tech). Application of both of these strategies to drug discovery is converging. Chemical synthesis strategies are often synthesized by introducing a variety of chemical modifications onto a central molecular structural platform (“scaffold”). Our work goes beyond the basic library synthesis method and involves the production of a scaffold family, i.e. a group of molecular platforms that share a common overall architecture but differ from each other incrementally. Conclusions: This poster describes the design and execution of synthesis methodology for the preparation of all possible versions of substituted piperazine-2-acetic acid esters derived from amino acids. Our methodology produces a scaffold family that is suitable as a starting point for the production both in FBLD and DEC-Tech, which are described in our accompanying posters. We call this strategy Systematic Chemical Diversity.

137 Exploration of drug-like chemical space and biological activity using piperazine based compound libraries Prashit Jain, Baylor College of Medicine; S. Chamakuri; E. Samuel; S. Guduru; I. Raji; C. Santini; D. Young

Introduction: “Chemical space” is the term used to denote the micro-environment that exists around drug-like compounds. (“Libraries”) of such compounds that incrementally differ from each other are an effective way of exploring the relationship between chemical structure and biological response (SAR; Structure Activity Relationship). Elucidating the details of SAR is at the very heart of cancer drug discovery. Most chemical leads that result in new medications are generated via costly high-throughput biochemical screening (HTS) using large (~10^6 member) libraries of fully elaborated drug analogs. Even with such large compound libraries the attrition rate of chemical leads is very high and is a major problem in early stage drug discovery. New strategies for lead identification have therefore been developed. Methods: One such strategy is Fragment Based Lead Discovery (FBLD). Fully elaborated drug molecules can be considered as a combination of smaller, simpler and more reactive molecular fragments. Such fragments can be produced by parallel synthesis as shown on an accompanying poster. Because fragments are smaller and simpler than fully elaborated drug molecules, fragment chemical space is much smaller than drug-like chemical space. Fragment screening requires fewer compounds (102-103) compared to HTS. Screening of these fragments, followed by chemical modifications, can afford new clinical agents. FBLD is now recognized as a cost-effective way to identify high quality leads in the quest for new therapeutics. Another strategy for lead identification is DNA encoded compound libraries (DEC). DEC is predicated on a more extensive coverage of chemical space. An accompanying poster describes DEC in detail. Results: Our research involves the synthesis and screening of piperazine based compound libraries derived using both strategies. Our piperazine scaffolds contain the elements that lend themselves to facile creation of molecular diversity with the goal of improving chemical space coverage and consequently, our chances of lead discovery success. This poster describes the elements that lend themselves to facile creation of molecular diversity with the goal of improving chemical space coverage and consequently, our chances of lead discovery success. This poster describes the elements that lend themselves to facile creation of molecular diversity with the goal of improving chemical space coverage and consequently, our chances of lead discovery success. This poster describes the elements that lend themselves to facile creation of molecular diversity with the goal of improving chemical space coverage and consequently, our chances of lead discovery success. This poster describes the elements that lend themselves to facile creation of molecular diversity with the goal of improving chemical space coverage and consequently, our chances of lead discovery success.

138 Construction of a diverse human antibody phage display library Robbie Schultz, The University of Texas Health Science Center at Houston; G. Salazar; N. Zhang; Z. An

Introduction: Phage display technology is a powerful tool for rapidly and efficiently generating a fully human monoclonal antibody library. Libraries of phage-displayed antibodies can then be used to isolate antibody fragments against specific antigens using a process of affinity selection called panning. Funded in part by the CPRIT Therapeutic Monoclonal Antibody Lead Optimization and Development Core grant (RP150551), we have constructed a highly diverse human antibody display library using phage-display technology. Methods: To maximize size and overall complexity, we...
created the library using memory B cells isolated from enriched peripheral blood mononuclear cells from multiple healthy donors. Variable regions of both heavy and light immunoglobulin were cloned and inserted into a large primer set. After amplification, the antibody genes were cloned and joined using a flexible linker to generate single-chain variable fragments in a phagemid vector system. The antibody fragments were then displayed on the surface of M13 phage to create a library with a diversity exceeding 10e11 surface displayed cDNA. Screening of this new high-throughput system showed that variable region gene usage reflects natural abundance within the human antibody repertoire. To date, the library has been used to isolate antibodies against multiple targets, including eight proteins and one peptide. **Conclusions:** In conclusion, we have created an antibody library using phage display technology that has successfully been used to isolate fully human monoclonal antibodies against a variety of targets. Due to its large size and complexity, our library is an ideal tool for selecting antibodies for multiple downstream applications, including potential therapeutic use.

**139**

**CPRIT Grantee Poster Session B**

**TRPM7 kinase domain rather than the channel regulates breast cancer cell migration and tumor metastasis**

**Soljung Yhm, The University of Texas at Austin; T. Kaoud; X. Xie; R. Mangieri; J. Park; C. Tavasoli; T. Jiang; Z. Lu; L. Devkota; E. Cho; K. Dalby**

**Introduction:** The channel-kinase TRPM7 (transient receptor potential melastatin 7) is a bifunctional protein consisting of a cation channel that is permeable to Mg²⁺, Ca²⁺ and Mn²⁺ ions fused to a C-terminal kinase domain. Studies of purified TRPM7 protein have suggested that TRPM7 is linked to adhesion and migration of breast cancer cells and promotes breast tumor metastasis. While the channel properties of TRPM7 have been studied extensively, little is known about the function of its kinase activity. **Methods:** To understand the functions of the kinase domain we identified the first cell-permeable inhibitor of the kinase domain (TRPM7-IN-1) and developed MDA-MB-231 breast cancer cell lines in which TRPM7 is knocked out by CRISPR/Cas9 (KO), and in which various forms of TRPM7 were stably re-expressed. These were wild type TRPM7 (WT), a kinase-inactive mutant of TRPM7 (KO), and TRPM7 containing a truncated kinase domain (KT). **Results:** Knock out of TRPM7 significantly inhibited MDA-MB-231 cell migration. Only expression of the wild type TRPM7 (WT) rescued the migration phenotype, supporting a role for the kinase domain in the regulation of cell migration. Magnesium deprivation, which promotes TRPM7 kinase activity, induces phosphorylation of eEF2, presumably to impede protein synthesis. Treatment of magnesium-deprived HEK293 cells with TRPM7-IN-1 decreased eEF2 phosphorylation, consistent with suppression of TRPM7 kinase activity in-cells. TRPM7-IN-1 decreased the binding of Myosin II to TRPM7 in HEK293 and MDA-MB-231 cells. And when MDA-MB-231 cells were transfected with cytochalasin D, TRPM7 phosphorylation of Ser-1569 and its downstream substrate Myosin IIB to TRPM7 in HEK293 and MDA-MB-231 cells. And when MDA-MB-231 cells were transfected with cytochalasin D, TRPM7 phosphorylation of Ser-1569 and its downstream substrate Myosin IIB were completely abrogated at a concentration of 5 µM. TRPM7-IN-1 inhibited MDA-MB-231 cell migration and invasion, while treatment of the KO cells with TRPM7-IN-1 showed no further inhibition of migration. **Conclusions:** In contrast to previous reports revealing that the inhibitor did not affect the channel function in MDA-MB-231 cells, supporting the notion that the inhibitor affects the migration exclusively through the inhibition of the TRPM7 kinase domain. Finally, in an experimental metastasis model, TRPM7-IN-1 significantly impeded metastasis to the lung. **Conclusions:** Inhibition of TRPM7 kinase activity may reduce or block breast tumor progression and/or metastasis.

**140**

**CPRIT Grantee Poster Session B**

**Identification of ENL YEATS domain inhibitors using a robust and cost-effective AlphaScreen assay**

**John Veloso, The University of Texas at Austin; A. Devkota; E. Cho; K. Dalby**

**Introduction:** The chromatin reading domain ENL YEATS has been linked to multiple cancers including breast cancer. These studies suggest that ENL YEATS proteins exhibit domain-specific functions that are critical for regulating gene expression and cell proliferation. In this report, we describe the development of an in vitro assay to screen libraries for ENL YEATS domain inhibitors. The AlphaScreen (Amplified Luminescent Proximity Homogeneous Assay Screen) detection platform, to identify novel molecules that disrupt ENL YEATS binding. **Methods:** To investigate a cost-effective AlphaScreen strategy, a high-throughput AlphaScreen (HTAS) platform was employed using the AlexaFluor® 647 dye labeled ENL YEATS domain with His-tagged ENL YEATS and biotin-H3K9Ac was employed as a model system. The binding assay of ENL YEATS (target protein) and H3K9Ac (substrate peptide) was initially established. In detail, the assays were performed in an assay buffer [50 mM HEPES pH 7.4, 100 mM NaCl, 1.0 mg/ml BSA, and 0.05% CHAPS] using 100 nM His-tagged ENL YEATS and 30 nM biotin-H3K9Ac. Assays were performed in 20 µL volume in white 384-well OptiPlates. The assay was read on an Envision plate reader equipped with a high-throughput AlphaScreen laser. All reactions were performed in subdued light conditions (<100 lux) and at ambient temperature. **Results:** We have determined that the concentration of Alphabeads can be reduced by 4-fold from 10 µg/mL to 2.5 µg/mL, and the concentration of peptide can be reduced by 3-fold without negatively affecting assay quality. Additionally, we observed that this new method does not alter the activity of the inhibitor when the HTAS platform is used. **Conclusions:** In summary, this new high-throughput AlphaScreen strategy shows promise as an excellent tool for rapid screening of compound inhibition between the two platforms. Furthermore, we have performed a primary screen of approximately 70,000 small molecules and have determined that the assay was robust, and produced z’, S/B, and S/N of 0.83 ± 0.08, 66.29 ± 23.19, and 22.45 ± 6.45, respectively. The screening methodology is amenable to nanomolar potency that are good leads for further pharmacological development. **Conclusions:** This new high-throughput, robust screening platform will be useful for identifying new inhibitors that interfere with chromatin reading proteins, and may help with the subsequent development of anti-cancer drugs targeting oncogenic gene expression.
**ABSTRACTS**

**ACADEMIC RESEARCH**

**Development of a lipidomics platform for cancer metabolism research**

**Poster Session B**

**CPRIT Grantee**

**Chun-Liang Chen, The University of Texas**

**Methods:** To explore the metabolic changes of cancer cell lines and in vivo studies, lipidomics analysis was performed using liquid chromatography time-of-flight mass spectrometry. The results showed that lipid metabolism is altered in cancer cells compared to normal cells.

**Results:** The lipid metabolites were significantly different between cancer cell lines and normal cell lines. The analysis revealed that cancer cells have an increased synthesis of lipids associated with lipid signaling pathways.

**Conclusions:** These findings suggest that lipidomics analysis can provide valuable insights into the metabolic changes that occur in cancer cells, which may have implications for the development of targeted therapies.

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**Structure-Based Drug Discovery in a Web Portal**

**Poster Session B**

**CPRIT Grantee**

**William Allen, The University of Texas at Austin**

**Methods:** The DrugDiscovery@TACC portal provides a virtual screening program that allows users to query a database of over 47,000 compounds and a library of 194,000 natural products. The program uses AutoDock Vina to perform molecular docking.

**Results:** The portal has been used to identify potential drug candidates for various diseases, including cancer. The results have been validated using in vitro and in vivo experiments.

**Conclusions:** The DrugDiscovery@TACC portal is a powerful tool for drug discovery and has the potential to accelerate the development of new therapies.

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**Castration resistance transcriptome in prostate cancer revealed by global RNA-seq data**

**Poster Session B**

**CPRIT Grantee**

**Lauri Lieberman, The University of Texas Health Science Center at San Antonio**

**Methods:** RNA-seq data from prostate cancer patients was analyzed using bioinformatics tools to identify gene expression changes associated with castration resistance.

**Results:** The analysis revealed that several genes linked to drug resistance were upregulated in castration-resistant prostate cancer.

**Conclusions:** These findings suggest that understanding the transcriptome of castration-resistant prostate cancer could lead to the development of new treatments.
Introduction: Fatal metastatic castration-resistant prostate cancer (mCRPC) remains without sensitive early detection biomarkers and effective therapeutic targets. Each year, about 30% of 149,000 newly diagnosed prostate cancer patients who will develop mCRPC while the other 70% may remain indolent not needing treatment. However, the PSA and other biomarkers are limited in distinguishing the aggressive mCRPC from the slow growing prostate cancer. Among 2.5 million prostate cancer patients, the major challenge is to identify those not to treat, as these patients are diagnosed at an early stage represent an unmet need. With early identification, clinicians could design new treatment strategies that can be designed to reduce metastatic potential and extend survival of patients.

In this study, we deployed single-cell RNA-seq on prostate cancer cells (LNCaP, ABL and PC3) to determine the transcriptomic systems in androgen independency and castration resistance of prostate cancer.

Results: We identified potential 336 androgen-independence specific genes and 2986 castration resistance specific genes in ABL and PC3 cells respectively, while only 136 genes were shared in both cells. These genes, mostly upregulated were enriched in 43 and 166 signaling pathways that implicated the complexity of the castration resistance transcriptomic systems and networks. The signaling pathways are involved in advanced and metastatic malignancies including TNF, TGFβ, TGFβ, STAT, EPHB, focal adhesion, adherens junction, regulation of actin cytoskeleton, gap junction, tight junction and EMT. Malignant potencies of ~ 40 pathways were validated by in silico analysis of the RNA-seq data from the prostate cancer cohort of The Cancer Genome Atlas (TCGA) using Kaplan-Meier disease free and survival curve analyses. The transcriptomic regulation of these genes was further validated and correlated with GRO-seq and ATAC-seq data. In order to further verify the functions of those signaling pathways in castration resistance, 9 major signaling pathways were evaluated using small molecule inhibitors. Castration-resistant prostate cancer cells showed significant defective cell proliferation, migration, invasion and sphere formation in the presence of inhibitors, whereas LNCaP and ABL cells displayed limited or non-significant changes. Interestingly, five small molecule inhibitors showed significant suppression on the growth of circulating tumor cells that were derived from clinical blood samples of prostate cancer patients.

Conclusions: Our data suggest that those castration resistance specific genes and signaling pathways revealed by single-cell RNA-seq may serve as potential markers and therapeutic targets.

147 CPRIT Grantee Poster Session B

Progestrone receptor regulation of mTOR signaling in pre-invasive breast cancer

Seah Harlig, Baylor College of Medicine; S. Grimm, N. Chemn; H. Villanueva, C. Callaway; A. Contreras; K. Rajapakse; S. Huang; C. Edwards

Introduction: Clinical and epidemiological data have established progesterone (P4) as a risk factor for invasive breast carcinoma (IBC). Ductal carcinoma in situ (DCIS) is a precursor to IBC that contains estrogen receptor (ER) and progesterone receptor (PR) expression. Despite the fact that the majority of DCIS are ER and PR positive, whether and how P4/PR influences the progression of DCIS to IBC are unknowns.

Methods: To address these questions we developed an experimental system by stable expression of ER and PR in a human comedo DCIS cell line. A combination of proteomics, gene expression profiling, and respirometry were used to explore the influence of P4 on molecular pathways and cellular processes in DCIS in vitro.

Results: DCIS COM cell lines expressing ER/PR were highly responsive to P4 exhibiting robust regulation of known PR target genes and an inhibition of proliferation. Microarray expression profiling and bioinformatics analysis of publically available data sets revealed gene signatures of ER/PR DCIS cell lines similar to that of luminal breast cancer, indicating the physiological relevance of our cell lines. Using a targeted reverse phase protein array (RPPA) proteomics platform, mTORC1 was identified as a predominant signaling pathway regulated by P4 that is of high interest because of its central role as an integrator of nutrient and growth signals that can enable high rates of protein synthesis required for survival of cancer cells. Additionally, constitutive activation of mTORC1 in DCIS and IBC is often reflected by a combination of PI3KCA mutations and aberrant growth factor signaling. P4 mediated activation of mTORC1 was validated by immunofluorescence staining that reflected on protein translation and higher glycolytic activity. We determined that P4 activation of mTORC1 occurs by transrepression of DEPTOR, a member of the mTOR complex that acts as an inhibitor of mTORC1 activity. By chromatin immunoprecipitation (ChIP) assay we identified intrinsic PR binding motif in the DEPTOR gene promoter region. We predicted that DEPTOR and mTORC1 signaling corresponded with P4 induced PR-DNA binding. Inhibition of mTORC1 activity with rapamycin amplified the growth inhibitory effects of P4 in DCIS cells, suggesting PR may collaborate with therapeutic vulnerabilities associated with PI3KCA

mutations and activated mTOR in breast cancer.

Conclusions: Targeting PR together with mTOR inhibitors may represent a new therapeutic avenue for prevention and management of breast cancer progression of pre-invasive to IBC.

148 CPRIT Grantee Poster Session B

The Gulf Coast Consortium Center for Advanced Microscopy

Information: Michael Callaway; Baylor College of Medicine; P. Davies; F. Stossi; A. Rao; L. Vergara

Introduction: The Center for Advanced Microscopy and Image Informatics (CAMII) is a multi-institutional, multi-disciplinary core facility designed to provide investigators from the Gulf Coast Consortium for Chemical Genomics (GCC) access to customized, project-driven, quantitative imaging-based solutions that support basic and translational cancer research. CAMII builds upon the recent success of a collaboration between the Texas A&M Institute for Biosciences and Technology (Houston campus) and Baylor College of Medicine to create a productive and efficient imaging program in the Texas Medical Center utilizing the sophisticated microscopy resources at both institutions. This successful collaboration has resulted in high impact publications and supported outstanding translational drug discovery research projects in GCC institutions; when combined with an overall increased interest in quantitative microscopy, the CAMII was designed to maximize support of outstanding cancer-relevant research in GCC. By providing unique imaging resources to both established and junior investigators, CAMII will support projects that are at the forefront of contemporary cancer research. In partnership with the GCC drug discovery CFSA programs, CAMII will also implement a drug discovery pipeline supporting promising lead drugs and antibodies from in vitro testing, to in vivo testing, and pre-clinical development.

Methods: The Specific goals include: 1) supporting meritorious projects by providing researchers with access to infrastructure and technical expertise to facilitate answering the most challenging questions of cancer biology and drug discovery; 2) facilitate development of new technologies and improvement of existing platforms to advance the field of imaging-based cancer research; and, 3) familiarize cancer researchers with the application of advanced imaging-based research technologies to projects that address the causes, prevention, and treatment of cancer. Results: Results from Center goals/projects will be achieved through the assembled support of a multi-disciplinary team of experts in imaging and imaging informatics operating a state-of-the-art core facility. CAMII is developing focused imaging platforms and informatics to support long-term live cell imaging studies, high resolution single cell analytics and high throughput/multiplexed drug screening. As a component of the Gulf Coast Consortium for Chemical Genomics, CAMII will join the GCC network of core facilities supporting cancer-related basic science and drug discovery research in the Texas Medical Center.

Conclusions: CAMII is committed to having a transformative impact on cancer research in Texas and contributing to the CPRIT’s goal of supporting innovation in cancer research and promoting breakthroughs in the cancer prevention and cancer cures.

149 CPRIT Grantee Poster Session B

Next-Generation Sequencing (NGS) Facility Core at MD Anderson Cancer Center Science Park

Jianjun Shen, The University of Texas MD Anderson Cancer Center; M. MacLeod; Y. Liu

Introduction: The development of NGS over the past eleven years has created a paradigmatic shift in our ability to probe the molecular details of cancer. These technologies allow much more complete analysis of the transcriptome and its regulation, the detection of rare “driver” mutations in cancer genomes, and the ability to quickly and comprehensively define features of the epigenome. Methods: With CPRIT funding in 2012, we established a regional NGS Facility Core with HiSeq 2500 and MiSeq instruments at MD Anderson Science Park, dedicated primarily to supporting cancer research in central Texas. We conducted extensive protocol development, quickly established all essential NGS protocols, and, 3) familiarize

CAMII is committed to having a transformative impact on cancer research in Texas and contributing to the CPRIT’s goal of supporting innovation in cancer research and promoting breakthroughs in the cancer prevention and cancer cures.
150

Comparison of ChIPSeq data prepared with different techniques and very low levels of input DNA

Methods: We evaluated the performance of ChIPSeq kits from four suppliers (Bioo, Diagenode, KAPA and NEB) at nanogram (ng) (10, 1, 0.1 and sub-ng [500, 250, 100 picogram (pg)]) by performing ChIP in LNCAP cells with antibodies against H3K4me3 (a marker of transcriptionally active chromatin that displays sharp peaks), H3K27me3 (a marker of transcriptionally repressed chromatin with broad enrichment domains) and CTCF (a transcription factor). Total H3 and Input were used as controls for quantification and normalization, respectively.

Results: Diagenode, KAPA and NEB kits maintained high library complexity that decreased at the 100 pg level, while libraries prepared by the Bioo kit exhibited lower library complexity than the others at all concentrations. For H3K4me3, all kits performed fairly well at each concentration, with the majority of samples having >75% of peaks called in promoter regions and around 50% of known promoters marked by sharp peaks. For H3K27me3, each library showed the expected broad enrichment domains except for the Bioo and KAPA kits at 100 pg. The peak intensity of each library negatively correlated with gene expression, with the Bioo kit having the highest peak intensity and CTCF kits having the lowest correlation. For CTCF, the Diagenode and KAPA kits had better performance than the Bioo and NEB kits, with a higher number of peaks called, a similar percentage of peaks identified with the CTCF motif, and a closer distance between the CTCF motif and the peak summit.

Conclusions: Our preliminary results suggest that the ChIP-Seq kits depend on which proteins are being studied but that none are sufficient for working with ≤100 pg DNA. Nonetheless, all of the kits we evaluated can be used when studying active histone modification such as H3K4me3 in sharp peaks. However, the Bioo kit is best when looking at repressive histone modification with broad enrichment domains, while either Diagenode or KAPA kits are best for transcription factors.

151

Cancer Proteomics and Metabolomics Core Facility

Methods: The main technology platforms of the Core Facility include 1) mass-spectrometry-based metabolomics, 2) mass-spectrometry-based proteomics, 3) targeted proteomics by antibody-based reverse phase protein array (RPPA) and 4) multi-omics integrative data analysis and bioinformatics. The core continues to advance cutting-edge technologies. Metabolomics has developed targeted assays for steady-state quantification of 650 known metabolites, isotopomer-based flux assays to trace activities of major metabolic pathways in cells, lipidomics for up to 300-400 molecules, and MS-2 unbiased metabolic profiling. Mass-spectrometry-based proteomics includes IP-MS analysis of protein complexes, a label-free quantitative method for unbiased profiling up to 5,000 proteins and profiling different classes of proteins, including the kinome, phospho-proteome and transcription factors. The RPPA platform provides highly sensitive robust quantification of 220 proteins representative of major oncogenic signaling pathways. Bioinformatics tools include workflow pipelines for management and analysis of large omics data sets and for developing omics platforms.

Results: Over the first five years of operation the Core Facility supported 256 projects for cancer researchers, and 76 publications, many in high impact journals such as Science, Nature, Cell, Cancer Cell and J. Clin. Investigation. The economic impact of the Core Facility includes awarding of 45 grants ($49M total) to users with preliminary data generated by the Core and/or specific aims requiring Core support. Scientific discoveries resulting from Core supported research projects includes identification of drivers of initiation and progression of different cancer subtypes, uncovering mechanisms of resistance to therapies, and identifying novel potential biomarkers for diagnostic and therapeutic targets. Some projects that identified new therapeutic targets have moved forward to the drug development stage.

Conclusions: This is a well-established and highly productive Core Facility that supports high quality basic cancer research projects for a broad range of investigators. Future goals are to continue to develop innovative technologies to advance the proteomics and metabolomics tools and to optimize procedures with patient specimens and increase throughput for clinical validation studies.

153

CPRIT Grantee Poster Session B

The Gulf Coast Consortium’s Combinatorial Drug Discovery Program

Introduction: Drug repurposing and combinatorial repurposing are cancer therapeutics strategies of great interest to clinical cancer researchers. Repurposing is important for cancer patients because it...
has the potential of identifying new therapies that can be “fast tracked” into clinical use without the long delays associated with getting “new” drugs approved for clinical use. High throughput library screening technologies, testing the activity of large numbers of combinations of clinically relevant drugs against the target cancer has the potential to accelerate the discovery of novel therapies for hard to treat cancers. To take advantage of this strategy investigators need access to the sophisticated core research support provided to conduct high throughput discovery research including: 1) a core facility that provides the complex technologic infrastructure to conduct high throughput cell-based screening and research and 2) a multi-disciplinary team of experts in high throughput drug discovery, imaging-based screening, image analysis and data informatics. The Gulf Coast Consortium’s Combinatorial Drug Discovery Program (CDDP), a CFSA-supported multi-institutional core facility is providing researchers with access to these key resources.

**Methods:**

Combinatorial drug discovery research requires a core facility providing the complex infrastructure necessary to conduct high throughput cell-based screening. The CDDP is fully equipped to run in vitro screens from single biochemical end points to live cell imaging using fully automated platforms. The core maintains a multi-disciplinary team of experts in the fields of high throughput drug discovery, imaging-based screening, image analysis and data informatics. **Results:** The CDDP’s is providing cancer researchers with access to compound/drug libraries, laboratory automation, specialized cell culture capabilities and imaging platforms, technical expertise and the informatics necessary for library-screening studies using advanced cellular models of cancer, and “fit for purpose” high throughput cell-based screening to support the discovery of novel therapies for cancer.

**Conclusions:** The CDDP’s value is reflected in the large demand for its services.

Core collaborators are incorporating many new advanced cellular models into their discovery projects with promising combinations can then be rapidly advanced to animal testing and subsequent clinical evaluation.

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**154 CPRIT Grantee Poster Session B**

**mRNA therapy for improved adoptive T-cell transfer**

Sahana Suresh Babu; Hung, M.; Miller, T.; C. Liu; F.; Mamonkin; J.; Thonhoff; S.; Appel; K.; Chen; M.; Brenton; I.; Bruno; J. Cooke; Z.; Chen; A.; Mamonkin; J.

**Introduction:** Cancer immunotherapy is a promising therapy for a wide variety of malignancies. An exciting approach of cancer immunotherapy is adoptive T-cell therapy, wherein the natural ability of T-lymphocytes to recognize tumor antigens and kill target cells is augmented. In normal human T-lymphocytes, extensive proliferation leads to replicative senescence; a constraint in the number of times that cells can divide. Replicative senescence is characterized by a reduction in telomerase (hTERT) activity and shortening of telomeres. This is an obstacle for T-cells engineered to express chimeric antigen receptors (CAR-T) therapies because the ex vivo expansion and expansion to achieve therapeutic doses of the CAR-T cells involves a stage of high proliferation. In this regard, an adoptive immunotherapy trial observed that telomere length of transferred lymphocytes correlated with in vivo T-cell persistence following treatment, suggesting that telomere length and the potential for repetitive T-cell expansion play a significant role in avoiding replicative senescence and thereby mediating a successful clinical response.

**Methods:**

Peripheral Blood Mononuclear Cells (PBMC) were isolated from the human donor blood followed by activation with CD3 and CD28 antibodies to selectively enrich T-cells in culture. High-performance liquid chromatography (HPLC)-grade therapeutic hTERT mRNA was produced in collaboration with the RNAcore production team. Nucleofection technology was employed to transfuse the HPLC-grade hTERT and other mRNA into T-cells. Viability and T-cells population were analyzed using flow cytometry following 24hr of mRNA transfection. We have generated the first preclinical evidence that transfection of hTERT mRNA increases T-cell replicative capacity in vitro, and improves efficacy of CAR-T approach against a murine model of human B-cell malignancy. We have further introduced hTERT to CAR-T cells directly against disialoganglioside (GD2), a surface molecule expressed in neuroblastoma and neuroectoderm-derived neoplasms. Our preliminary data indicate that hTERT mRNA transfected GD2 CAR T cells show an increased cell number and also telomere length compared to controls. We further aim to develop a novel codon-optimized RNA-based reagent for delivery of mRNA hTERT TCRs in human T-cells. Constructs of hTERT mRNA have shown potential to improve the therapeutic benefits of CAR-T therapy. In collaboration with our bioinformatics team, we have also developed optimal codon algorithm for mRNA stabilization in human T-cells. We further aim to develop a novel codon-optimized RNA-based reagent for delivery of these hTERT mRNA TCRs in human T-cells.

**Conclusion:**

We have developed mRNA therapy for improved adoptive T-cell transfer. The results demonstrate that hTERT mRNA has shown potential to improve the therapeutic benefits of CAR-T therapy. In collaboration with our bioinformatics team, we have also developed optimal codon algorithm for mRNA stabilization in human T-cells. We further aim to develop a novel codon-optimized RNA-based reagent for delivery of these hTERT mRNA TCRs in human T-cells.

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**155 CPRIT Grantee Poster Session B**

**Targeted therapeutic drug discovery program (TTP) for integrated, collaborative, high-throughput drug development**

Eun Jung Cho; G.-H. Yoon; S. Zhang; J.-H. Lee; A. Devkota; J. Veloria; R. Edupuganti; J. Lee; C. Zhang; P. Ren; K. Dalby

**Introduction:** With an increasing understanding of the molecular pathways underlying cancers, translational & clinical investigators are identifying molecular targets at an increasing rate. The challenge for these investigators is having access to the specialized resources and experiences that are necessary to support robust drug development efforts, especially those focused on the early development phase encompassing the validation of good molecular targets and the design & development of chemical entities that meets the targets for pre-clinical studies. This is a critical gap that the Targeted Therapeutic Drug Discovery & Development Program (TTP) has been designed to fill, which provides a holistic drug discovery and development stream to help investigators identify potential new drugs. **Methods:** We offer four highly integrated modules to realize a fully cohesive platform for advancing new molecules from ‘discovery’ to animal testing. These are i) a compound screening module, which supports assay design and implementation, to identify molecules for potential lead optimization, as well as data management and follow up mechanistic support. ii) a chemistry module which supports structure-guided synthesis of new analogs, as well as the scale up of lead synthesis. iii) a chemoinformatics & modeling module which a) supports the development of preliminary Structure Activity Relationships (SAR) for hit compounds, as well as the identification of structurally similar commercially available analogs via structure-based docking or pharmacophore searching and b) supports advanced in silico modeling and early prediction of ADMET properties. iv) a lead characterization module which provides access to structural biology facilities and pharmacokinetic expertise. **Results:** We have developed an integrated pipeline to provide translational scientists with collaborative support for the development of new drugs to advance to clinics. Projects benefit by collaborating with TTP at various stages within the pipeline.

**Conclusions:** We believe our integrated drug discovery platform will increase the number of new compounds in Texas reaching the stage of preclinical testing that possess the potency, selectivity and pharmacokinetic parameters needed to enter clinical development.

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**156 CPRIT Grantee Poster Session B**

**Gulf Coast Consortium for Chemical Genomics: a multi-institutional network of core facilities to support cancer-related drug discovery and development**

Suzanne Tomlinson, Gulf Coast Consortia for Quantitative Biomedical Science; C. Schwen; K. Dalby; Z. An; M. Mancini; M. Matzuk; D. Jiang; S. Weidman; P. Dalby

**Introduction:** Since 2001, the Gulf Coast Consortia for Quantitative Biomedical Sciences (GCC) has been a very successful multi-institutional academic collaborative network composed of research and clinical faculty from seven member academic institutions in the Houston/Galveston area. One of these consortia, the John S. Dunn GCC Consortium for Chemical Genomics (GCC CG) is focused on the development of research infrastructure and core facilities to support and promote cancer-related drug discovery and development.

**Methods:** Harnessing original momentum generated through the award of a CPRIT-funded multi-institutional Multi-Investigator Research Award (MIRA; the Texas Screening Alliance for Cancer Therapeutics), the GCC CG has now developed 1) an extensive state-wide network of academic and clinical cancer researchers with projects spanning the entire drug development pipeline; 2) a web-based application and project tracking portal, 3) rigorous review and communication processes; 4) exceptional educational workshops and conferences focused on cancer therapeutics discovery and development, and 5) new collaborative partnerships to support the development of cancer therapeutics.

**Results:** With the decline in drug development in pharmaceutical companies, TTP assumes significant responsibility by serving as a preeminent incubator and development facility providing the complex infrastructure necessary to conduct high throughput drug discovery, imaging-based screening, image analysis-based and research technologies that are collaborating to provide a network of research resources that can be deployed to accelerate the discovery and development of new cancer therapeutics. The basic concept is that by seamlessly sharing access to critical resources across institutional boundaries without constraint, the network can provide the most efficient and effective support for the development of new cancer therapies.

**Conclusions:** With the decline in drug development in pharmaceutical companies, TTP assumes significant responsibility by serving as a preeminent incubator and development facility providing the complex infrastructure necessary to conduct high throughput drug discovery, imaging-based screening, image analysis-based and research technologies that are collaborating to provide a network of research resources that can be deployed to accelerate the discovery and development of new cancer therapeutics. The basic concept is that by seamlessly sharing access to critical resources across institutional boundaries without constraint, the network can provide the most efficient and effective support for the development of new cancer therapies.
CPRIT Core Facility

Program, the Therapeutic Monoclonal Antibody Lead Optimization and Development Core, and most recently the GCC Center for Advanced Microscopy and Image Informatics) are working together to promote and support cancer-related therapeutics research. Three new GCC core facilities, GCC Center for Comprehensive PK/PD and Formulation, the Center for Computer-Accelerated Therapeutics, and the High Throughput Immunosensitizer discovery Core are under development to expand the ability of the network to support drug development projects, extending the pipeline of support to move the most promising therapeutic candidates to preclinical and clinical testing. Conclusions: By developing new core resources that “fill” existing “gaps” and networking new and existing therapeutics discovery and development resources into a “cancer resource core network,” GCC CG continues to advance CPRIT’s goal to move discoveries through development and ultimately to the bedside.
**157**

**CPRIT Grantee Poster Session A**

**Risk prediction for Barrett's esophagus and esophageal adenocarcinoma: incorporation of epidemiologic risk factors and 23 confirmed genetic loci**

**Jing Dong, Baylor College of Medicine; M. Buas; T. Vaughan; S. Zhao; A. Thrift**

**Introduction:** We developed comprehensive risk prediction models for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) that incorporate a polygenic risk score (PRS) and non-genetic variables. **Methods:** We used data from 3,288 BE, 2,511 EAC, and 2,177 controls from BEACON, the United Kingdom Barrett's Esophagus Gene Study, and United Kingdom Stomach and Oesophageal Cancer Study. A PRS was created from 23 BE/EAC risk loci. We developed and compared risk models with various combinations of non-genetic factors and the PRS. We assessed their predictive accuracy by dividing the area under the receiver operating characteristic curve (AUC). **Results:** Individuals in the highest quintile of the PRS had 2-fold higher risks of BE (odds ratio [OR], 2.22; 95% confidence interval [CI], 1.89-2.60) and EAC (OR, 2.46; 95% CI, 2.07-2.92) compared to those in the lowest quintile of the PRS. Risk models including only demographic/lifestyle factors (age, sex, smoking, body mass index, and nonsteroidal anti-inflammatory drugs) or only gastroesophageal reflux disease (GERD) symptoms had AUCs ranging from 0.637 to 0.687. The AUCs for models adding demographic/lifestyle factors to GERD symptoms were 0.793 and 0.745 for BE and EAC, respectively. Small but significant improvement in AUCs for each model was observed when including the PRS in the model (AUCs range, 0.656-0.799; all P < 0.001). Including the PRS in the model of non-genetic factors provided 3.0% and 5.6% improvement in the net reclassification index for BE and EAC, respectively. **Conclusions:** Risk prediction models that combine non-genetic and genetic information may be useful in identifying high-risk populations of BE and EAC for targeted cancer prevention.

**158**

**CPRIT Grantee Poster Session B**

**Multi-Objective Optimization based Biomarker Discovery**

**Zhandong Liu, Baylor College of Medicine; Y. Wan; H. Jin; M. Anderson; C. Mach**

**Introduction:** Discovering molecular pathways determining patient response to treatment is a critical step towards developing effective cancer therapies. To this end, huge databases of genomic, molecular, and clinical data from large cohorts of cancer patients continue to be assembled by major national and international projects. Multiple measures of disease response often exist, but yet do not provide equivalent insight. Unfortunately, only a small fraction of the information available in the majority of high throughput databases has been effectively used. **Methods:** To combine multiple types of clinical variables and protein-protein interaction networks, we formulated the MPA model through the multi-task learning framework. The first part of the objective function of MPA is a weighted sum of log-likelihood functions on each clinical variable. The first variable is typically treated as binary and hence will be modeled using logistic regression with binomial link. In contrast, duration of survival is a continuous variable without censoring, hence we will use the cox proportional hazards model, which only has a partial likelihood function. A normalization factor is used to ensure that the log-likelihood functions are balanced. The group L2 norm penalty requires the solution for each clinical variable to be similar, but ensure that the log-likelihood functions are balanced. The group L2 norm penalty requires the solution for each clinical variable to be similar, but also to be connected on the protein-protein interaction network. The L1 norm penalty enforces model sparsity, namely only a small set of genes will be selected and the rest will be set to zero. The network smoothness penalty enforces the solution to be connected on the protein-protein interaction network. **Results:** To evaluate the performance of MPA and identify pathways predictive of patient response to treatment, we applied our method to the Level 3 TCGA ovarian cancer dataset. MPA identified predictive sub-networks to both chemotherapy and overall survival. Anaplastic lymphoma kinase (ALK) is the hub gene in the largest sub-network. Using the identified ALK sub-network by our model, we were able to compare patients into chemoresistant and chemosensitive groups. These two groups demonstrate significant survival differences. We transfected OVCAR3 cells with either an shRNA targeting ALK or a non-targeting control. Our results clearly indicate that knockdown of ALK expression sensitizes OVCAR3 cells to platinum chemotherapy, reflected by a 2-fold increase in the IC50 for cisplatin. These results demonstrate that MPA can effectively combine multiple types of clinical variables and protein-protein interaction networks to identify key pathways most important for driving the growth and progression of cancer.

**159**

**CPRIT Grantee Poster Session A**

**Functional Hallmarks of Acute Myeloid Leukemia from Cellular Images**

**Cecilia Lantos, Rice University; S. Kornblau; A. Qutub**

**Introduction:** Acute myeloid leukemia (AML) is a devastating blood cancer, with only a 25% patient survival rate. Characterizing AML is a challenge because no single gene or sets of genes define the disease. To address this heterogeneity, proteomic screening of AML cells has supplemented genomics, enabling a new class of molecules to be identified as potential therapies and helping improve clinical trial design. However, translating the proteomic work to the clinic is a long-term endeavor requiring the use of new screening methods. Here we introduce work towards a novel, computational approach to map common histological screening to the AML patients’ underlying proteomics signatures. **Methods:** Prior research in our lab has identified key protein signatures predictive of AML patient response to chemotherapy, overall survival and remission duration. However, proteomic screens are expensive and non-standard. AML diagnosis and therapy are currently based on morphological classification of patients’ bone marrow cells, and genetic abnormalities. The goal of this study is to apply the prognostics of the proteomic data to the clinic near-term, by developing methods to computationally map the proteomic signatures to a common clinical measure: histological analysis. The proposed project optimizes techniques that recognize cellular phenotypes from bone marrow histology slides and mathematically defines how protein signatures relate to cellular morphology. Using pattern recognition techniques, machine learning and deep learning modeling approach, the morphological cellular data of AML histology image or series of histology images and underlying genetic **Conclusions:** Results of this work will speed up the diagnosis of AML and advance personalized therapy for the heterogeneous blood cancer. The methods developed during this study can be applied directly to routine clinical biospies for AML to rapidly support personalized, precise therapy, and potentially uncover new pathways for drug targeting.

**160**

**CPRIT Grantee Poster Session B**

**Risk of Hepatocellular Cancer in Patients with Non-alcoholic Fatty Liver Disease in Texas**

**Jennifer Kramer, Baylor College of Medicine; F. Kanwat; S. Mapakshi; Y. Natarajan; M. Chayanupatkul; P. Richardson; L. Li; R. Desiderio; A. Thrift; H. El-Serag**

**Introduction:** Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease including hepatocellular carcinoma (HCC) in the U.S. Texas has the highest age-adjusted HCC rates nationwide. However, there are limited data on the risk of HCC in NAFLD in Texas. **Methods:** This was a retrospective cohort study from patients seen at a facility in the Veterans Health Administration (VHA). Veterans with NAFLD diagnosed between 1/1/2004 and 12/31/2008 were included and followed until HCC diagnosis, death or 12/31/2015. We defined NAFLD as evidence of ≥2 elevated ALT values >6 months apart, with no evidence of HBV and HCV or alcohol abuse. We also identified a gender and age-matched control cohort without NAFLD or other risk factors for liver disease. We ascertained all new HCC cases in both cohorts from the Cancer Case Registry and manual chart reviews. We calculated the annual incidence rates for HCC by NAFLD status as well as in subgroups of NAFLD patients. We used a proportional hazard model adjusted for competing risk of death to examine the effect of NAFLD on risk of HCC while adjusting for other confounders. **Results:** We compared 31,815 NAFLD patients from Texas with 31,815 controls. NAFLD patients were significantly more likely to be Hispanic (15.3% vs 4.2%), obese (53.8% vs 35.2%), have diabetes (27.3% vs 19%), hypertension (66.9% vs 8%), dyslipidemia (66.0% vs 53.1%), and end-stage renal disease (2.7% vs 0.4%) than controls. During 255,550 person-years (PY) of follow-up, 81 NAFLD patients developed HCC for an incidence rate of 0.32/1000 PY. This rate was significantly higher than controls (0.03/1000 PY) and NAFLD patients from the US overall (0.19/1000 PY). The risk of developing HCC was 8.9-fold higher in NAFLD than controls (hazard ratio=8.84, 95% confidence interval=4.22-18.52). Among patients with NAFLD, those with cirrhosis had the highest annual incidence of HCC (9.6 vs. 0.10/1000 PY in patients without cirrhosis). Male and Hispanic NAFLD patients also had a higher HCC incidence rate (0.45/1000 PY vs 0.34/1000 PY for women, ratio=1.34, 95% CI=1.02-1.76; 0.43/1000 PY). **Conclusions:** Risk of HCC was higher in NAFLD patients from Texas than that observed in general clinical population and NAFLD patients from US overall. The absolute risk of HCC was higher than the accepted thresholds for HCC surveillance for patients with NAFLD cirrhosis.

**161**

**CPRIT Grantee Poster Session A**

**Oxygenation Response to Hypoxic Gas Breathing in Rat Breast Tumor**

**Ralph Mason, The University of Texas Southwestern Medical Center; K. Arri; J. Campbell; G. Gerber; H. Zhou; L. W. Cutler**

**Introduction:** Hypoxic sites in breast tumors are targets of new therapeutic strategies using hypoxia activated prodrugs. A prerequisite for evaluating this therapy is to establish breast tumor animal models with alterable degrees of hypoxia. Herein, we use oxygenation-sensitive MRI to investigate the changes in hypoxia profile in rat 13762NF tumors during respiratory challenges. **Methods:** Subcutaneously implanted 13762NF tumors (n = 15) were given hypoxic (16% O2) and hyperoxic...
Introduction: Fluorescence imaging of tumor structural, functional and molecular information has been widely investigated and is playing an important role in preclinical cancer research and clinical cancer diagnostics. It has high sensitivity and specificity with benefits of low cost, use of non-ionizing radiation and capability of multiplex imaging. However, fluorescence imaging suffers from limitations in different applications. For example, fluorescence microscopy has high spatial resolution (sub-micrometer), but the limited depth and tissue diffuse optical tomography can image tissue as deep as several centimeters but is limited with poor spatial resolution (a few millimeters). Ultrasound is another commonly used medical imaging modality and has relatively high resolution with a penetration depth of several centimeters. While ultrasound is more dependent on acoustic impedance mismatch, it is insensitive to tissue (bio)chemical or molecular features. X-ray based CT has very high spatial resolution, but is limited by its poor sensitivity to soft tissues. Methods: To achieve high spatial resolution of fluorescence imaging while maintaining its unique features, such as high sensitivity and multi-color imaging, a new hybrid imaging modality, ultrasound-switchable fluorescence (USF) imaging, was recently developed, which overcomes the limitations and achieves high-resolution fluorescence imaging in centimeter deep tissue. In USF imaging, an excellent USF contrast agent and a sensitive imaging system are required. Different types of USF contrast agents have been synthesized and characterized. Several USF imaging systems have been developed. Results: High-resolution USF imaging in centimeter-thick tissue phantoms and in-vitro tissue samples has been very successfully achieved. Simultaneously imaging multiple targets via multi-colored USF significantly improves the specificity and sensitivity of fluorescence imaging of mouse organs and in-vivo USF imaging of mouse tumors have been studied and demonstrated. A commercial micro-CT is used to validate USF images in tissue-mimic phantoms, ex vivo tissue samples and in vivo mice with breast tumors. The results indicate that USF can accurately image tissue samples of different sizes and maintain high sensitivity and multi-color imaging capability. The 3D USF and micro-CT images match well and the quantitative comparison will be presented. Conclusions: USF can provide high resolution imaging with fluorescence contrast, which will be very useful for cancer structural, functional and molecular imaging with high sensitivity and specificity in the future.
high levels of glycolysis, are indicative of tumorogenesis. Through in vivo and ex vivo metabolic assays, we sought to show that tumor metabolism correlates with and can be predictive of tumor aggressiveness. **Methods:** Mice were intracranially injected with patient-derived glioma sphere-forming cells (GSC). The six GSC lines have established genomic profiles and produce distinct survival times in mice. Tumor development was followed with T1-weighted, T2-weighted, and fluid-attenuated MRI. At specific time points throughout tumor progression, hyperpolarized 13C MRI experiments were performed to measure the dynamic metabolic flux of pyruvate to lactate in the tumor which is an important metabolic event at the end of glycolysis. Following in vivo hyperpolarization experiments, the mice were euthanized and their brains excised. Tumor samples were lysed to extract the water-soluble metabolites, and the global, steady-state metabolite concentrations in each GSC line were measured with nuclear magnetic resonance (NMR) spectroscopy. **Results:** An initial cohort of mice (N=5) has been imaged to completion. Tumor growth and mouse survival curves have been established and MRI pulse sequences optimized for follow-up studies. In the hyperpolarization experiments, the most aggressive GSC tumors produced the highest real-time flux of pyruvate to lactate, while the least aggressive tumors possessed the lowest flux. We have quantified the concentrations of 25 metabolites from NMR analysis of ex vivo tumor samples and are in the process of identifying the specific metabolic pathways that are affected in the different GSC lines. **Conclusions:** This initial study demonstrates the capability of hyperpolarized MRI to non-invasively measure tumor metabolism in order to stratify GSC-derived tumors based on their aggressiveness. The next step is to evaluate the utility of this approach in vivo in animal studies, which is to correlate the in vivo hyperpolarization data with T1-weighted, T2-weighted, and fluid-attenuated MR images and corresponding ex vivo NMR metabolomics data.

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**167**

**CPRIT Grantee Poster Session A**

**Surfaceome profiling enables isolation of cancer-specific exosomal cargo in liquid biopsies from pancreatic cancer patients**

**Vincent Bernard of Texas A&M University System Health Science Center:**

J. Castillo; F. San Lucas; K. Allenson; M. Capello; D. Kim; M. Katz; G. Varadharachy; M. Javel; H. Alvarez; A. Maitra; S. Hanash

**Introduction:** Detection of circulating tumor DNA (ctDNA) can be limited by its relative scarcity in circulation, particularly while patients are actively undergoing therapy. Exosome-positive cell-free tumor DNA can be enriched from liquid biopsies and can provide a tumor-derived ctDNA. One important finger print in mechanical phenotyping is cell deformability. One important finger print in mechanical phenotyping is cell deformability. To measure the undeformed cell size, velocity and deformation index of each channel enabling us to increase the throughput (>100 cells/sec). High speed video-imaging and automated image processing allows us to measure the undeformed cell size, velocity and deformation index of each cell. We use these readouts to phenotype highly metastatic (MDA-MB231), lowly metastatic (MCF7) and non-tumorigenic (MCF10A) breast epithelial cell line MCF10A. The flow conditions are chosen such that these cell lines experience enough fluid shear to deform them. A microfluidic manifold was designed to apply the same driving pressure to each channel enabling us to increase the throughput (>100 cells/sec). High speed video and automated image processing allows us to measure the undeformed cell size, velocity and deformation index of each cell.

**Methods:** Our newly engineered device contains a dozen constricted microchannels of hydraulic diameter slightly bigger than the mean size of breast cancer cell lines MCF7 and MDA-MB231 and non-tumorigenic breast epithelial cell line MCF10A. The flow conditions are chosen such that these cell lines experience enough fluid shear to deform them. A microfluidic manifold was designed to apply the same driving pressure to each channel enabling us to increase the throughput (>100 cells/sec). High speed video and automated image processing allows us to measure the undeformed cell size, velocity and deformation index of each cell. We use these readouts to phenotype highly metastatic (MDA-MB231), lowly metastatic (MCF7) and non-tumorigenic (MCF10A) breast cell lines. We also evaluate how these readouts vary with cytoskeletal inhibitors, to measure the undeformed cell size, velocity and deformation index of each cell.

**Conclusions:** By using high-throughput microfluidic devices that use shear induced deformation of adherent cancer cell lines in narrow microchannels to phenotype them.

**168**

**CPRIT Grantee Poster Session B**

**A nanoprobe-based strategy for gastric cancer detection in PDX mice model**

**Xinyi Zhang, The University of Texas Southwestern Medical Center:**

G. Huang; C. Liu; J. Lian; Y. Li; H. Huang; J. Gao

**Introduction:** Despite its declining incidence, gastric cancer is still among top 5 of the most prevalent cancers globally. Incidence and mortality rates remain high in Asia and Latin America. With a library of ultra-pH sensitive (UPS) polymer nanoprobes, we are able to utilize the acidic and angiogenic tumor microenvironment to achieve detection of the tumor in its early stage. Here we test this possible application in mouse model of gastric cancer. Engraft PDX tissue onto mice, each carrying two tumors on bilateral flanks. After tumors grow to desired size, inject intravenously polymer (ethylene glycol)-b-poly(ethylene glycol)-b-poly(2-dimethylaminoethyl methacrylate) copolymer (PEG-b-PEPA), or poly(ethylene glycol)-b-poly(2-dimethylaminoethyl methacrylate) copolymer (PEG-b-PDPA) at different pHs. Scan tumor fluorescence image at different pHs. The nanoprobe dual pH sensitive nanoprobes light up tumor quite well without much signal in normal tissues except liver and spleen where nanoparticles are cleared.

**Conclusions:** UPS nanoprobes are useful tools to help with the detection of tumor when used during gastric cancer operation, it can potentially show up metastatic sites and aid the surgeon to clear all of the cancer sites.

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**169**

**CPRIT Grantee Poster Session A**

**Salivary S100P Protein as a Potential Biomarker for Oral Cancer Detection**

**Yi-Shing Cheng, Texas A&M University System Health Science Center:**

L. Jordan; H. Chen; T. Rees

**Introduction:** Salivary S100P Protein as a Potential Biomarker for Oral Cancer Detection.

**Conclusions:** UPS nanoprobes are useful tools to help with the detection of tumor when used during gastric cancer operation, it can potentially show up metastatic sites and aid the surgeon to clear all of the cancer sites.
which further supports S100P being a cancer biomarker. However, whether the level of S100P protein is also elevated in OSCC patients’ saliva was unknown. Therefore, the purpose of this study was to measure the salivary levels of S100P protein in OSCC patients and compare with levels found in CP patients. Methods: Saliva samples were collected from a total of 121 human subjects from four study groups: OSCC (n=30); CP-S (Smokers with CP, moderate to severe degree, n=31); CP-NS (Non-smokers with CP, moderate to severe degree, n=31); and Healthy Controls (n=31). Levels of S100P protein were determined by enzyme-linked immunosassay (ELISA), and normalized by total salivary protein level, which was determined by bicinchoninic acid (BCA) assay. Normalized S100P protein levels between each pair of patient vs. non-cancerous groups were analyzed by independent ttests and ANOVA with Scheffe post hoc tests, because data distribution was found to be normal and had equal variance. Results: S100P protein showed significantly higher levels in OSCC patients compared to both CP-NS patients (p=0.002), and the Healthy Controls (p=0.001). S100P protein levels in OSCC patients were higher than those found in CP-S, but not at a statistically significant level (p=0.091). There was no significant difference in S100P protein levels between CP-S and CP-NS patients (p>0.05) or Healthy Controls (p=0.858); and no significant difference between CP-NS patients and Healthy Controls (p=0.05). Conclusions: Salivary S100P protein appears to be a promising biomarker for OSCC detection in individuals without CP and in CP patients who are non-smokers. Smoking, in the presence of CP, appears to raise salivary S100P protein to a level approaching that in OSCC patients. A one-step PCR method to detect the NPM-ALK protein in peripheral blood samples instead of by painful, invasive tissue biopsies.

170

CPRIT Grantee Poster Session B

High resolution microendoscope to improve early detection of bladder cancer Imran Vohra, Rice University; K. Cherry, T. Quang; Y. Tang; J. Cams; R. Schwarz; N. Dhanani; R. Richards-Kortum

Introduction: Bladder cancer is the 6th most common cancer in the United States. When detected early, bladder cancer can be treated successfully. However, bladder cancer has a high rate of recurrence, and as a result, is the most costly cancer to treat. Standard cystoscopic surveillance has several shortcomings; many bladder cancers appear as small, subtle, flat lesions that are difficult to distinguish from benign changes. While endoscopic technology and imaging can improve sensitivity, there is an important need to improve the ability of cystoscopy to characterize lesions as benign or malignant with high specificity. We report the development and initial evaluation of a high-resolution microendoscope (HRME) to characterize bladder lesions during cystoscopy. The HRME is a low-cost (~$3,000) fiber-optic microscope that provides images with subcellular resolution in real time, revealing morphologic detail that is traditionally only available following biopsy and histology. The HRME has received an investigational device exemption from the FDA but has not been FDA-approved for clinical use. Methods: Bladder specimens scheduled to undergo standard of care cystoscopy were recruited for in vivo imaging at Lyndon B. Johnson Hospital in Houston, Texas. Imaging was performed in the operating room during cystoscopy. In addition, bladder specimens were obtained through a tissue bank for ex vivo imaging. A preliminary analysis was performed to explore the microscopc appearance of bladder lesions using a high-resoultion IHC system to distinguish precancerous and cancerous lesions from non-neoplastic tissue. Results: To date we have imaged 11 patients in vivo and 7 bladder specimens ex vivo using the HRME. Preliminary results indicate that cell nuclei are larger, more crowded, and more erratically shaped at lesion sites than in normal bladder tissue. These images and results are comparable with published images and results obtained by other groups using commercially available confocal microscopes that cost on the order of 50x as much as the HRME. Conclusions: To the best of our knowledge this ongoing study represents the first use of a low-cost, high-resolution imaging platform to this end. The ability to image microscopic morphologic features to characterize bladder lesions in real time may have the potential to assist in the early detection of bladder cancer.
Etiology/Early Detection/Diagnosis

175

Genome-wide profiling of DNA methylation in peripheral blood leukocytes and prostate cancer aggressiveness

CPRIT Grantee Poster Session B

Chisara M. Williams-Tsaal, The University of Texas M.D. Anderson Cancer Center; W. Chang; J. Gu; Y. Han

Introduction: DNA methylation at CpG sites plays important roles in cancer development and progression. Hypomethylation of the promoter regions of tumor suppressor genes leads to gene silencing whereas global hypomethylation may affect chromosome structure and cause genomic instability. The goals of this study are to investigate the role of global DNA methylation in prostate cancer aggressiveness and identify CpG site methylation as predictors of aggressive prostate cancer.

Methods: We measured global DNA methylation level of long interspersed nucleotide elements (LINE-1), pericentromeric repeat (NBL2), and subtelomeric repeat (D4Z4) in leukocytes and determined their associations with clinicopathological variables at diagnosis and biochemical recurrence (BCR) upon active treatments. We also used Illumina's HumanMethylation450 beadchip to profile DNA methylation wide CpG site methylation in leukocytes and analyzed their associations with prostate cancer aggressiveness.

Results: There was no significant differences in the methylation level of LINE-1, NBL2 and D4Z4 between clinically defined aggressive and non-aggressive PCs at diagnosis. LINE-1 and NBL2 methylation was not associated with BCR either. However, the methylation of subtelomeric region D4Z4 was associated with BCR. We found that patients with higher methylation of D4Z4 exhibited an increased risk of BCR in localized patients receiving definitive therapy. In tertile analysis, patients in the highest tertile of D4Z4 methylation had an increased risk of BCR (HR=2.17, 95% CI, 1.36-3.46) compared to patients in the lower tertiles after adjustment of age, BMI, smoking status, pack year, D’Amico risk groups, and treatments. Among the four CpG sites we measured in this region, the association was mostly attributable to the methylation of the 2nd CpG site of D4Z4. When analyzing individual CpG site methylation, we identified a number of CpG sites which were distinguishably aggressive from non-aggressive prostate cancer and found a CpG site methylation signature that can identify a subgroup of patients with aggressive prostate cancer.

Conclusions: These data suggest that methylation in the subtelomeric region D4Z4 may be able to predict a CpG site methylation signature that can identify a subgroup of patients with aggressive prostate cancer.

176

Filipodia dynamics as a potential label-free biomarker for detection of highly metastatic cancer cells

CPRIT Grantee Poster Session B

Jose C. Contreras-Naranjo, Texas A&M University; A. Jayaraman; V. Ugaz

Introduction: Detection of highly metastatic cancer cells is critical for patient prognosis and treatment when performing single cell analysis, for instance, in rare cells isolated from blood in a liquid biopsy. Filipodia, thin (200-400 nm) “finger-like” plasma membrane protrusions, have emerged as important contributors to cancer metastasis and could reveal the presence of these cells. Reflection interference contrast microscopy (RICM) is used here for label-free imaging of filipodia-like structures in cancer cells of different metastatic potential (e.g., PC3 and LNCaP) as their label-free biomarker. Four previous reports illustrate the potential for detection of highly metastatic cancer cells using filipodia dynamics as a label-free biomarker.

Methods: Prostate cancer cells with high (PC3) and low (LNCaP) metastatic potential were maintained under RPMI medium with 10% fetal bovine serum at 37°C. 50k cells were used for each experiment. Cells were detached by Trypsin-EDTA, centrifuged down and re-suspended in fresh media. RICM images, recorded every ~10-15 s over ~1.5-2.5 h after loading cells into a microchamber, were obtained using a Zeiss Axiosvert 200M inverted microscope with a Zeiss Antiflex EC Plan-Neofluar 63x/1.25 Oil Ph3 objective, X-Cite exact light source (546 nm monochromatic light), and maximum illumination numerical aperture.

Results: Close cell-glass interaction (<~40 nm) is eventually observed in most cells, with PC3s consistently forming a more well-defined adhesion patch. The adhesion behavior, readily accessible to RICM with its “view from above” perspective, is easily hidden in blood cells, where no apparent changes in cell morphology are evident. During the adhesion process, PC3 and LNCaP cells probe their environment with filopodia-like structures, which are easily visualized when producing bright intensities (possibly corresponding to filopodia-substrate separation ~100-150 nm). A color-coded composite RICM image of maximum intensities for a given adhered cell enables visualization of its filipodia dynamics “fingerprint”. Despite similar size and sphere-like morphology, PC3 cells exhibit a higher degree of activity and highly uniform substrate probing using filopodia when compared to LNCaP cells. A RICM-based label-free analysis of PC3 and LNCaP’s adhesion and filipodia dynamics, although semi-quantitative in the current stage, allows filipodia-based discrimination between these cell lines. Further research, using blood cells and cells with high/low metastatic potential from different cancer sites, is necessary to enable the development of an integrated diagnostic platform for liquid biopsy analysis. In such platform, the filipodia dynamics “fingerprint” of isolated rare cells will be probed with RICM for label-free detection of highly metastatic cancer cells.
Providing rich molecular information with similar molecular patterns to those detected in tissues. We are continuing to analyze FNA samples to identify the value of DESI-MSI for preoperative diagnosis of thyroid lesions. Conclusions: DESI-MS was used to identify molecular markers of follicular thyroid tumors for rapid clinical diagnosis of FNA biopsies.

Molecular Targeting of MUC1 in Colorectal Cancer Using Hyperpolarized Magnetic Resonance Imaging of Silicon Particles

Introduction: Hyperpolarized silicon nano- and microparticles are potentially well-suited to act as targeted molecular imaging agents due to their unique biological behavior and hyperpolarized signals. In this study, dynamic nuclear polarization was performed on silicon particles functionalized with an antibody to MUC1, a mucin glycoprotein that is aberrantly expressed in colorectal cancer. Antibody conjugation to the particle surface did not affect 31Si hyperpolarization characteristics. Conversely, the dynamic nuclear polarization process did not hamper the targeting ability of the antibody. In vivo magnetic resonance imaging was performed 5 min after particle administration into humanized MUC1-expressing orthotopic colorectal cancer mouse models, and indicated the particles actively targeted the tumor sites. These results were evaluated by chemical and histological analysis and correlating immunohistochemical analysis. These surface-functionalized silicon particles are under development as a platform technology that will allow non-invasive molecular targeting of colorectal cancer using hyperpolarized magnetic resonance imaging. Methods: Antibodies (MUC1-targetted or control) were conjugated to silicon particles of various sizes (200 nm or 70 nm) and subjected to dynamic hyperpolarization using a specialized apparatus. These particles were tested for their ability to specifically bind to MUC1-expressing colon cancer cell lines in vitro or early stage colon tumors in mice harboring the human MUC1 gene. Detection in mouse colon was done using standard MRI methods. Results: Antibody conjugated silicon micro or nanoparticles retained both their ability to become hyperpolarized with a sustained (> 40 min) signal as well as to specifically target MUC1 expressing colon cancer cells in vitro or in vivo. Conclusions: That were targeted to control antibodies to target these cancer cells or tumors and MUC1-targetted particles did not bind to normal colonic epithelia. These particles can be hyperpolarized and retain specificity and robust hyperpolarization signal following the hyperpolarization procedure. This approach can potentially be used to target other cell surface antigens not only in colon cancer, but also in other cancers as a new early detection method.

Hyperpolarized Magnetic Resonance Imaging of Silicon Particles

Introduction: We have developed a microfluidic platform capable of performing precise isolation of micron-scale particles and cells. Our design uniquely merges the most favorable aspects of (1) continuous operation at high flow rates (nL/min range) with (2) the high selectivity of a physical membrane barrier. Preliminary results demonstrate size-based isolation and enrichment of cancer cells from whole blood with throughput 1 – 2 orders of magnitude faster than currently possible, while simultaneously preserving viability. Methods: Human prostate cancer cell line PC3 obtained from ATCC was maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 µg/mL streptomycin. PC3 cells were incubated under a humidified 5% CO2 atmosphere at 37°C. PC3 cells were then stained with CellTracker Red CMTPX and spiked into fresh human blood (K2 EDTA anticoagulant). The ratio of blood cells and PC3 cells were adjusted by addition of phosphate buffered saline solution to achieve expected abundance of WB and PC3 cells. Cells were obtained using a Multiuser 3 Coulter counter (Beckman Coulter), and confirmed with a hemocytometer. Erythrocytes were lysed with Zap-oglobin II lytic reagent (Beckman Coulter) for determination of leukocyte and cancer cell counts. The harvested PC3 cells were observed and imaged under fluorescence microscopy (Axiovert 200M, Carl Zeiss) with 63X objective. Cells numbers are expressed with respect to the total collected sample volume. Viability was assessed using trypan blue exclusion. Results: Whole blood spiked with PC3 human prostate cancer cells (20 – 30 µm dia.) was injected into the inner lane of the microfluidic separation device at flow rates up to 1 ml/min. Phosphate buffered saline (PBS) was co-injected into the outer lane at the same flow rate. Injected component densities were PC3: 1.43 x 10^8 cells/ml and PBS: 10^9 cells/ml.
10^6 cells/mL, WBC: 1.22 x 10^7 cells/mL, RBC: 7.32 x 10^6 cells/mL. Cell counts indicate that FC3 cells were separated with > 99% efficiency with 1.6x enrichment from the recovery from 3.5 cm deep in the lymph node tissue, with a yield of 10^6 cells/mL. These cells were maintained in the as-injected blood environment with no discernable change in viability (before filtration: 98.7% ± 0.6%, n = 3; after filtration: 98.9% ± 0.1%, n = 3). Conclusions: Separation efficiencies up to 80% are achievable with single-stage filtration. The recovery rate of > 3 x 10^6/mL is making this approach well suited for high-throughput processing of large sample volumes.

181 CPRIT Grantee Poster Session A

Improving the identification of genomic allelic imbalance (GAI) in multisamples, tumor-only studies using synthetic normals Jerry Fowler, The University of Texas M.D. Anderson Cancer Center; F. San Lucas; S. Sivakumar; T. McDowell; E. Ehli; G. Davies; P. Scheet

Introduction: Tumor genomic characterizations are typically performed by comparing the genomes of tumor samples to genomes of paired-normal samples. However, there are a variety of common scenarios in which matched normal samples are not available. In mutation detection, this is commonly addressed by comparing tumor samples to the reference human genome for variant detection and then applying filtering algorithms to remove likely germline events. Study designs are evolving however, and the use of mutation samples through the cancer-region multi-region sampling is becoming more common. Here we devised a strategy to improve somatic aberration detection in multisample, tumor-only studies by generating “synthetic normal” samples. Given multiple tumor samples, we aggregate putatively normal components of each sample’s genome into a surrogate normal genome to allow for computational tumor-normal analyses. Our initial focus here is on improving allelic imbalance (AI) event detection in such studies, but the concept is also applicable to mutation and copy number profiling. Methods: We called genotypes for 163 samples from 29 non-small cell lung cancer patients using the Illumina GSA array. We characterized AI events using hapLOH, which detects regions of haplotype imbalances. Conventionally, these haplotypes are inferred using paired-normal samples, but this study lacked such samples. Thus, we inferred haplotypes and called AI events using 3 different strategies: (1) analyzing samples independently, (2) identifying the “most normal” sample for each patient and treating that sample as a surrogate paired-normal, and (3) aggregating high-quality genotypes for all samples of an individual into a “synthetic normal” for use in AI calling. Results: Numbers of heterozygous genotypes increased from strategies 1 to 3, resulting in improved haplotype estimation and a higher number of AI event calls. There were two scenarios in which AI sensitivities were improved: (1) where complete cn-LOH was observed, and (2) where there was variability in genotype quality within a patient’s samples. In the first case, heterozygous genotypes were recovered where previously long stretches of haplotypes were imputing. In the second case, artificial synthetic normals provided increased genotype densities across the genomes of lower-quality samples, improving power to detect AI. Conclusions: The synthetic normal concept provides a strategy for dealing with tumor-only analyses in settings where multiple samples are available from single individuals. We demonstrated its benefit in AI profiling using fibroblasts and myofibroblasts 0.85 and 0.80, respectively. Conclusions: GA-LDA provides an effective method for dimension reduction of FTIR images. In addition, this algorithm provides features that are viable for DFIR imaging and provide high accuracy when tested against alternative approaches. While GA optimization is generally time-consuming, our GPU-based approach addresses this by taking advantage of data-parallel computation on an inexpensive local workstation. Classification based on spectral signature provides high accuracy for cancer-relevant tissue types, better than PCA on complex data sets. This also enables use selected spectral markers for Discrete Frequency IR (DFIR) imaging.
185
CPRIT Grantee Poster Session A
Label-free classification of infrared images of tumor biopsies using convolutional neural networks
Sebastian Berisha, University of Houston; M. Walsh; D. Marenich
Introduction: Histopathology continues to be the main tool utilized in the diagnosis of cancer. The current methods for cancer detection rely on the examination of a biopsy tissue by a pathologist, after the tissue has been processed (including clinical staining). Even though these methods continue to remain the gold standard, the procedure is subject to error (staining quality) and non-quantitative. Fourier Transform Infrared (FTIR) spectroscopic imaging provides quantitative chemical and spatial information that allows the extraction of both biochemical composition and morphology information in a noninvasive manner. The absorbance spectra obtained via FTIR spectroscopy provide biochemical fingerprints for each pixel in the imaged tissue, which can be used for classification. FTIR imaging coupled with advanced machine learning tools may offer the potential for histopathological recognition without the use of dyes, probes, or human interpretation. Convolutional neural networks (CNNs) are the current method-of-choice in image classification in a machine learning framework. They can learn interpretable representations of the data. Methods: Traditional FTIR image classification methods rely only on the spectral information of an individual pixel to perform classification. In our approach, a CNN is trained using a local tensor region around the classified pixel. This allows the classifier to utilize the local spatial information embedded in the infrared image. CNN training is performed using multiple annotated tissue micro-arrays obtained from AMSbio consisting of cancer biopsies as well as adjacent normal samples. Training is performed using TensorFlow on a GPU accelerated server. Classification accuracy is then validated on separate annotated tissue microarrays. Results: When compared to traditional classification methods using a Random Forest on individual spectra, a CNN with utilizing spatial information exhibited performance gains from 10% to 15% on the same images with improvements in ROC curve areas across classes. This demonstrates a significant improvement over the individual spectra, with additional cost for image acquisition. Conclusions: We show that CNNs can be efficiently used to classify biomedical FTIR spectroscopic data. Our CNN-based method outperforms standard classification algorithms used in FTIR spectroscopy, such as random forests and decision tree-based classifiers, in terms of accuracy when applied to independent test data. We report classification results and analysis by applying a CNN architecture to data from tissue micro-arrays consisting of five cell types, namely blood, collagen, epithelium, necrosis, and myofibroblasts. Our results demonstrate the application and efficiency of deep learning algorithms in improving the diagnostic techniques in clinical and research activities related to cancer.

186
CPRIT Grantee Poster Session B
Clinical Language Annotation, Modeling and Processing Toolkit (CLAMP) for Extraction of Tumor Attributes in Cancer Pathology Reports
Erzin Soyasal, The University of Texas Health Science Center at Houston; J. Wang; H. Xu
Introduction: Natural Language Processing approaches have been successfully applied to cancer-related data requirements, since exponentially increasing data size and information exchange requirements make it crucial to use computational methods to process clinical narratives. Pathology reports are gold standards in cancer diagnosis, which holds the most important information for cancer management decisions. A set of cancer-specific components created for CLAMP to extract tumor attributes can be used in pathology reports embedded in a set of state-of-art natural language processing components to process pathology reports that were embedded into an integrated development environment to visually develop custom algorithms specific to clinical information requirements. Knowledge resources required by these applications consisted of dictionaries, section header list or medical abbreviation list were provided with the toolkit. CLAMP components were fine-tuned to use with pathology reports, including a set of tumor-specific information such as morphology, tumor grade, tumor location (topology) and procedure. Results: CLAMP can successfully be utilized in pathology reports of cancer patients by contributing to extract valuable tumor information. CLAMP promises an easy to use desktop application without sacrificing functionality. It serves a complete set of components to achieve the best possible results for clinical natural language processing, with the best proven approaches using a mixture dictionary based, rule based and machine learning methodologies.

187
Poster Session A
Image improvement in digital breast tomosynthesis
Nikolai Slavine, The University of Texas Southwestern Medical Center; S. Seiler; R. Lenkinski
Introduction: To evaluate in clinical use a novel rapidly converging, iterative deconvolution method to enhance contrast and image resolution in digital breast tomosynthesis. Methods: The method was tested on clinical breast imaging data. Data acquisition was performed on a commercial Hologic Selenia Dimensions breast tomosynthesis system. This method was additionally applied to patient breast images previously processed with Hologic software to determine improvements in resolution and contrast to noise ratio. Results: In all of the patients’ breast studies the improved images proved to have higher resolution and contrast as compared with images obtained by conventional methods. Conclusions: A rapidly converging, iterative deconvolution method with a resolution subbands-based approach that operates on patient DICOM images has been used for quantitative improvement in digital breast tomosynthesis. The method can be applied to clinical breast images to improve image quality to diagnostically acceptable levels and will be crucial in order to facilitate diagnosis of cancer progression at the earliest stages. The method can be considered as an extended Richardson-Lucy algorithm with multiple resolution levels.

188
Poster Session B
A Database of Cancer Associated SNPs in DNA Repair Genes (CSNP-DNAR)
Pavel Silvestrov, University of North Texas; G. Cisneros
Introduction: Cancer is a complex disease that can involve concurrent mutations in different cell compartments and can be caused by mutations in various genome locations. DNA repair enzymes play an important role in maintaining DNA integrity, and thus ensure faithful propagation of genetic information. Furthermore, cells that result from the carcinogenesis processes depend on DNA repair enzymes for further growth. Therefore, it is of particular interest to study the mutations that occur in DNA repair genes and to analyze their possible links to various types of cancer. Methods: We will present the development of a new database, CSNP-DNAR. The aim of this database is to provide a comprehensive compendium of mutations on DNA repair genes statistically linked to various cancers. To achieve this, we have collaborated with data on the structural manifestations of these mutations in DNA repair proteins. Results: Initial results will be presented, including a number of SNPs that translate into missense mutations in ALKBH7, and POLL genes. Computational simulations based on molecular dynamics of ALKBH7 and POLL provide insights on how the respective cancer variants affect these proteins’ structure and function. Conclusions: A better understanding of structure and function of the DNA repair genes is a good ground for development of cancer diagnostic and treatment methods.
Etiology/Early Detection/Diagnosis

190 Poster Session B
Predictive Ability of Sialic Acid Measured by Surface-Enhanced Raman Spectroscopy in Early Stage Breast Cancer
Ekaterina Vinogradova, The University of Texas at San Antonio; H. Navarro-Contreras; A. Hernandez-Artega; J. Zereno Nava; E. Kolosovas-Machuca; J. Velazquez-Salazar; M. Jose-Yacamán

Introduction: In the United States, breast cancer (BC) is the most common non-skin-related type of malignancy in women and is the second leading cause of cancer death in women. Early-stage detection of breast cancer (stages 0, I and II) through screening plays a crucial role in saving women’s lives as well as in reducing devastating emotional, physical and economic impacts of advanced stage cancer treatment. While screening mammography is currently the best available screening method for early detection of BC, it is associated with the harmful effects of ionizing radiation and its benefits are not the same for all women. Using physical and economic impacts of advanced stage cancer treatment.

Methods: Using the genotype and expression data from The Cancer Genome Atlas (TCGA), we performed systematic and large-scale investigation of both cis- and trans-eQTLs in multiple cancer types. Combined with TCGA clinical data, we further analyzed eQTLs which are associated with different survival and. To help interpreting disease-associated loci, we also mapped these eQTLs to GWAS loci. Results: We identified cis-eQTLs-gene pairs and 231 210 trans-eQTLs-gene pairs from 916 tumor samples in 33 cancer types. We further performed survival analysis and identified 2212 eQTLs associated with patient overall survival. Furthermore, we linked the eQTLs to GWAS data and identified 337 131 eQTLs overlap with existing GWAS loci. We developed PancanQTL, a user-friendly database (http://bioinfo.lifesci.hust.edu.cn/PancanQTL/), to store cis-eQTLs, trans-eQTLs, survival associated eQTLs and GWAS related eQTLs for searching, browsing, and downloading. Conclusions: In summary, we systematically identified cis-eQTLs, trans-eQTLs, survival associated eQTLs, and GWAS related eQTLs in 33 cancer types. We constructed a user-friendly database, PancanQTL, for users to query, browse, and download cis-eQTLs, trans-eQTLs, and GWAS related eQTLs. Kaplan-Meier plots were provided for scientific usage. PancanQTL will serve as an important resource for human cancer genetics and provide opportunities to bridge the knowledge gap from variants in sequence to phenotypes. Acknowledgement: UTHealth Innovation for Cancer Prevention and Research Training Program-Doctoral (Cancer Prevention and Research Institute of Texas grant # RP160015). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.

191 Poster Session A
Hepatocellular Carcinoma Screening is Underused in Patients with Cirrhosis
Debra Choi, Texas A&M University System Health Science Center; H. Kum; S. Park; R. Ohsfeldt; A. Singal

Introduction: Hepatocellular Carcinoma (HCC) incidence and mortality are rapidly increasing in the United States. Implementation of routine HCC screening is crucial for early tumor detection and curative treatment receipt to mitigate HCC mortality. Our study’s aim was to characterize utilization of HCC screening among at-risk patients in the United States. Methods: We conducted a retrospective cohort study using SEER-Medicare linked data among patients (n=11,659) diagnosed with HCC between 2006 and 2011. Patients were required to have continuous enrollment in Medicare Part A and B for ≥3 years prior to HCC diagnosis. We excluded patients enrolled in Medicare health maintenance organization. Results: We defined a subset of patients with known cirrhosis (n=1,836) based on ICD-9 codes. The primary outcome of interest was receipt of HCC screening over a 3-year period, which was defined using two measures. We first used three mutually exclusive categories: 1) consistent screening 2) some screening and 3) no screening. Consistent screening was defined as having ≥1 abdominal ultrasound per calendar year; some screening was defined as having ≥1 abdominal ultrasound but less than annual. Our second measure was proportion of time up-to-date with screening (PUTD): PUTD was defined as the proportion of the 36-month study period in which patients had received screening. We assessed screening receipt using claims for abdominal ultrasound within the 3-year surveillance period prior to HCC diagnosis. In a sensitivity analysis, we applied a validated algorithm to infer when ultrasounds were done for purposes of HCC screening. Most (60%) of ultrasonograms were not time-stamped or having consistent screening, with only 35% (n=4,110) having some screening and 47% of those who did not receive screening (p<.0001). The subset of patients with known cirrhosis had similarly low rates of consistent screening at only 9%; however, there were higher rates of screening at 51%. The mean PUTD was 10.4% ± 18.5%, although this decreased to only 3.8% ± 11.8% after accounting for screening intent. Conclusions: HCC screening is underutilized in the United States; likely contributing to high rates of late stage diagnosis and poor survival.

192 Poster Session B
Nanophosphors: Highly Sensitive Reporters for Smartphone-Based Diagnostics
Richard Willson, University of Houston; A. Paterson; B. Raja; V. Mandadi; B. Townsend; M. Lee; H. Goux; A. Dantharanyar; B. Vu; K. Kourentzi; J. Bigoch

Introduction: The lateral flow immuno-chromatographic assay (LFA), more commonly known as the home pregnancy test, is ideal for point-of-care diagnostic testing because of its low cost, simplicity, and freedom from elaborate and costly instrumentation. Inorganic phosphorescent materials exhibiting persistent luminescence are commonly found in electroluminescent displays and glowing paints but are not widely used as diagnostic agents. Persistent luminescence offers advantages over conventional photoluminescent probes, including the potential for enhanced sensitivity by collecting time-resolved measurements or images with decreased background autofluorescence while eliminating the need for expensive optical hardware, superior resistance to photobleaching, amenability to quantitation, and facile bioconjugation schemes. Methods: We have introduced persistent luminescent nanophosphors produced by grinding, sizing and silica-coating “glow-in-the-dark” SrAl2O4:Eu2+,Dy3+ powder as LFA reporters. Nanophosphors are first briefly excited with the phone’s camera flash, followed by switching off the flash, and subsequent imaging of nanophosphor luminescence with the camera. Results: Using this approach, we demonstrated LFA detection of human chorionic gonadotropin with strontium aluminate nanoparticles as reporters, giving a detection limit of ~45 pg/mL (1.2 pm) in buffer, 50-fold better than the detection limit of the average commercial pregnancy test. Conclusions: We have demonstrated LFAs based on persistent luminescence strontium aluminate nanoparticles. The extremely bright and long-lived emission of persistent nanophosphors allows sensitive analyte detection with a smartphone app by a facile time-gated imaging on a smartphone can be readily adapted for sensitive and potentially quantitative testing using other point-of-care formats, and is workable with a variety of persistent luminescent materials. Future work with phosphorescent strontium aluminate and other persistent luminescence materials could lead to a new class of reporters for diagnostics and environmental monitoring.
ABSTRACTS
ACADEMIC RESEARCH

193 Poster Session A
Multivalency design of VEGFR targeting molecular probe for tumor imaging
Zhen Yang, Houston Methodist; F. Li; Z. Li

Introduction: Designing ligands that exhibit specific binding to tumor targets is highly desirable in the molecular imaging of tumors. The strong correlation between angiogenesis and tumor growth provides vascular endothelial growth factor receptors (VEGFR) exceptional targets for the tumor imaging and therapy. Despite a variety of anti-angiogenic drugs approved by FDA, early detection of tumors is still limited. This is due to the improvement of their specificity to tumor targets. In this work, we present a multivalency design strategy to remarkably enhance the specificity of vandetanib compound to VEGFR. The developed vandetanib tetramer exhibits 1000-fold improvement in specificity to VEGFR compared to the FDA-approved monomer. This work not only provides a promising anti-angiogenic agent for tumor imaging and even therapy, but also demonstrates a multivalency design strategy for tumor-targeting molecular probes.

Methods: Adhesion force measurement of atomic force microscopy was used to decipher the binding force of vandetanib ligand to VEGFR on live human umbilical vein endothelial cells. Then the spatial distribution information of VEGFR on live cells was calculated, which guided the right design of multivalent vandetanib compounds. The imaging probes were synthesized via organic chemistry. Results: Using the right architecture design for the multivalency, the vandetanib tetramer exhibits 1000-fold improvement in specificity to VEGFR compared to its FDA-approved monomer. Conclusions: Multivalency is a powerful strategy in the design of imaging probes for tumor targeting. The single-force measurement design could work as an universal design platform for tumor targeting compounds. The designed vandetanib tetramer provides a promising anti-angiogenic agent for tumor imaging and even therapy.

194 Poster Session B
Micro-thermal sensor technology for non-volatile fluids and cellular level thermal conductivity measurement
Rohini Allam, University of North Texas; R. Shrestha; D. Simmons; T. Choi

Introduction: Cancer is the leading cause of death worldwide and, for 2017, U.S. cancer statistics project 602,900 deaths and about 1.7M new cancer cases diagnosed. However, when cancer can be diagnosed early survival rates improve dramatically. Traditional diagnostic tools for cancer screening include clinical/physical examinations, endoscopy, X-ray and various forms of imaging and magnetic resonance imaging (MRI). Still, these existing techniques are not very powerful methods in detecting cancer at very early stages. Researchers have extensively focused their studies in two mainstream fields: biomarkers and micro/nano-technology to develop powerful diagnostic methods for detection of cancer at early stages. The few research works that investigated the thermal properties at tissue level use transient hot wire technique and use thermal properties as a biomarker for cancer diagnosis. Yet, due to the size of commercially available sensors (>25 µm), measurement at the cellular level has not been possible. Therefore, we herein propose and test a unique technique that utilizes: a. A 2-D axisymmetric model created to determine the transient temperature profile for the experimental conditions. Through MATLAB algorithm, a multi-parameter minimization method was used to determine the optimizing parameters (conductivity, laser power) that will fit the simulation result with the experimental data. The transient conductivities of each material are compared with known values for error calculation. Results: The thermal conductivities for the 3 test fluids: 50% glycol, 70% glycol and water, evaluated as 0.3448, 0.2717 and 0.5938 W/m.K, respectively, were within 2% of their literature values. Conclusions: We demonstrate the capability of the sensor by testing 3 different fluids with known properties and determine their thermal properties with an accuracy of <2%. This technique can be used to measure thermal properties of group/individual normal and cancer cells to develop an early diagnostic method for cancer.

195 Poster Session A
Ecological Model-generated hypothesis for high prostate cancer incidence in African-Americans: TRPV6a gene variant and calcium-ion hypersensitivity
Constance Hilliard, University of North Texas

Introduction: Latest medical research identifies over-consumption of calcium as a trigger for metastatic Prostate Cancer. However, the fact that African-American males suffer twice the rate of fatal cancer as Caucasians continues to confound researchers. This is because 75% of Black are lactose-intolerant and have been identified as calcium-deficient, by Federal nutritional standards. African-American males consuming low-lactose dairy products have a calcium intake considered insufficient by American standards yet constitute four times the intake of their African ancestors. Thus, the evolutionary advantage in 200 million years is probably related to high calcium absorption capacity of their ancestral TRPV6a genetic variant of the TRPV6 calcium ion channel.

Methods: This EMS mines and synthesizes retrospective data from multidisciplinary scientific methods to produce a data profile that captures (1) geographical mapping TRPV6a, TRPV6b genetic populations (2) metastatic Prostate Cancer: triggers, genetics, epigenetics: (ii) Black/White differences: TRPV6 function, calcium retention, homeostasis (iii) TRPV6 gene, TRPV6a/TRPV6b polymorphisms and related genes, free calcium-ion retention rates (3) historical/ecological investigations of Prostate Cancer susceptibility rates, (4) regulatory guidelines: male calcium intake. Cox proportional hazards regression models were used to estimate the relative risks and 95% confidence intervals for Blak's Whites developing metastatic prostate cancer as a function of calcium consumption. Results: Use of this EMS reveals 17% of Black males diagnosed with metastatic Prostate Cancer consume 400 mg calcium/day while zero Black males exhibit this level. At 900 mg calcium intake/day 64% Black Americans, 41% White Americans, have developed the disease. 100% of the Black incidence of advanced Prostate Cancer will occur a/on below 1150 mg calcium intake/day in sharp contrast to 41% White incidence. Conclusions: This Ecological Model System identifies the TRPV6 gene as a therapeutic target for metastatic Prostate Cancer, thus posing clinical and basic research questions, e.g., “Can the use of TRPV6 calcium channel blockers and restrictions of dietary calcium reduce the African-American male risk profile? Is there a divergent mechanism of action of TRPV6 variants and regulation of calcium homeostasis that can identify additional targets?” Furthermore, results demonstrate the feasibility of EMS as a scientific approach to generate evidence-based hypotheses, stimulate new research questions and collaborations in population driven studies.

196 Poster Session B
Multimodal optical imaging for early detection of oral cancer
Kristen Maltland, Texas A&M Engineering Experiment Station; J. Jo; Y. Cheng; J. Wright

Introduction: Several optical technologies are available as clinical adjuncts to improve detection and identification of oral cancers and pre-cancerous lesions. This study, current system (i) Multispectral FLIM and high resolution RCM designed to access the oral cavity. Multispectral FLIM detects biochemical and metabolic changes using endogenous fluorescence lifetime imaging (FLIM) and reflectance confocal microscopy (RCM), the morphology and sensitivity and specificity adequate for early detection of oral cancer and dysplasia.

Methods: We have developed handheld endoscopes for macroscopic FLIM and high resolution RCM designed to access the oral cavity. Multispectral FLIM detects biochemical and metabolic changes using endogenous fluorescence of structural proteins and metabolic cofactors. 1 cm field of view FLIM images are acquired in 0.5 sec. RCM provides information on subcellular morphology. RCM videos with 800-micron field of view are acquired at 6 frames per second scanning ~200 microns into the tissue. Multispectral FLIM and RCM endoscopes prior to excisional tissue biopsy, which is processed for histopathology for diagnostic purposes. Results: Endogenous multispectral FLIM images were acquired from clinically suspicious oral lesions of 70 subjects undergoing tissue biopsy. The results indicate that mild dysplasia and early stage oral cancer could be detected and distinguished from benign lesions using confocal and multispectral FLIM. The results indicate that the FLIM was estimated using a cross-validation approach, showing levels of sensitivity >90%, specificity >80%, and area under the receiver operating curve >0.9. RCM videos were acquired from oral lesions in 16 subjects. Although only 2 imaging sites were diagnosed as dysplasia in this limited dataset, the FLIM videos and RCM findings correlated with biochemical features of the oral mucosa in vivo. Conclusions: Precancerous lesions can be heterogeneous, and show clinical features with many other nonprecancerous oral conditions, complicating accurate diagnosis.
ABSTRACTS

Etiology/Early Detection/Diagnosis

of pre-malignancy. Therefore, development of sensitive and specific clinical tools to aid detection and identification of pre-malignancy and cancer will improve the overall screening process. If this technology proves successful, it may enable real-time detection of premalignant and malignant oral mucosal lesions, surgical margin detection, and treatment monitoring.

197  Poster Session A
Characterization of Monoclonal Antibodies reactive to HPV-positive Head and Neck Cancer  Hsuan-Chen Liu, Baylor College of Medicine; A. Sikora; F. Parikh; T. Kraus; T. Moran

Introduction: Head and neck cancer (HNSCC) is the 6th common cancer in the world. While HNSCC caused by its traditional risk factors, tobacco and alcohol, has declined in Western countries, HNSCC caused by the human papillomavirus (HPV) are among the fastest growing cancers. Currently, there are no effective clinically-approved therapeutic reagents. Due to the unique biology of HPV infection, there is no targeted therapy approach for HPV-driven cancer. Our ongoing efforts focus on the identification of antigens on the cell surface of the host proteins that are altered by HPV infection. We present an “antigen-agnostic” approach for generating monoclonal antibodies as a potential tool for HPV-induced cancer diagnosis and treatment which does not require advance knowledge of the identities of target antigens. Methods: Immunogenic membrane vesicles made of HPV-positive head and neck squamous cancer cells (HNSCC) were used to immunize mice for generation of hybridomas by conventional methods. The supernatant produced by the hybridomas and/or purified antibodies were collected and screened for binding specificity with multiple HPV-positive cancer cell lines (2 HNSCC and 2 Cervical Cancer) and HPV-negative cancer cell lines (4 HNSCC and 1 CC) by Flow Cytometry. As an alternative approach to enriching for antibodies binding exclusively to HPV-driven membrane proteins, we generated an inducible HPV E6/E7 expression construct as a tool for hybridoma screening and understanding HPV-regulated biology. Results: Five thousand hybridoma colonies were picked up as potential candidates, after the initial screening of the supernatant for SCC-47 cells; results revealed 44 monoclonal antibodies that were specific to SCC-47 were identified. We have identified seven which preferentially bind to HPV-positive cancer cells; furthermore we have identified the binding targets of two clones, 6D8 and 6B3, via immunoprecipitation and mass spectrometry. These targets are integrin alpha6 (ITGA6) and tissue factor (F3) respectively. We validated the inducible HPV E6/E7 expression construct by qPCR and western-blot; unfortunately, we haven’t identified the clone that specifically binds to HPV E6/E7 overexpressed cells. Conclusions: Our screenings of mAbs have revealed promising candidates that bind selectively to HPV-driven HNSCC. Future work will validate the biological function of these mAbs in in vitro and in vivo models, and continue identifying additional mAb binding targets. We propose mAbs specifically targeting membrane-expressed antigens on HPV-related cancer cells as a potential tool for clinical use and preclinical research. It is anticipated that these HPV-specific mAbs could supplement imaging methods for early diagnosis of HNSCC and other HPV+ cancers.
Early detection of pancreatic cancer by targeted molecular MRI imaging of hyperpolarized silicon nanoparticles

Shivandar Pudakalakatti, The University of Texas M.D. Anderson Cancer Center; N. Whiting; J. Hu; C. McCowen; D. Carson; C. Farach-Carson; P. Pepe

Introduction: Pancreatic cancer, one of the leading causes of cancer-related deaths in Texas in 2016, is an aggressive and initially insidious lethal disease that develops relatively symptom-free. The absence of early symptoms and lack of a reliable screening test has created a critical need for developing a new noninvasive imaging strategy for pancreatic cancer early detection. The goal of my research project is to develop a noninvasive Magnetic Resonance Imaging (MRI)-based in vivo molecular imaging modality to detect pancreatic cancer at an early stage with high sensitivity and specificity. The high sensitivity is achieved by hyperpolarized (HP) Silicon nanoparticles (SiNPs) by Dynamic Nuclear Polarization (DNP) that leads to high-order enhancement. In contrast to the hyperpolarization of carbon-13 nucleus, by hyperpolarized Silicon nanoparticles (SiNPs) by Dynamic Nuclear Polarization (DNP) that leads to high-order enhancement. The presence of MUC1 in these transgenic mice enhances signal and longer decay of hyperpolarized signal. The optimized SiNPs are employed to non-invasively image the human MUC-1 expressing cancer cells in these animals to track the tumor progression from precursor lesion, PanIN to pancreatic cancer.

Conclusions: Targeted molecular imaging of pancreatic cancer progression with hyperpolarized SiNPs is feasible in vivo.
screen HRE in the 2015 MAUDE. For unstructured data, we compared six popular classification algorithms on the filtered reports by using term frequency and inverse frequency (TF-IDF). Then, we applied a word co-occurrence-based topic model that learns information from word combinations to further improve the best classifier of the six.

**Results:** Inclusion (132) and exclusion (21) keywords were selected to filter potential HREs. By applying the filter, 4,671 reports were identified from the 2015 MAUDE database. Then, 16 international experts randomly reviewed 10% of the identified reports and estimated that 50-60% of the reports were HIT-related, an improvement over the original 0.1%. The classifier combing TF-IDF and topic modeling features further improved identification based on the filter and thereby proposed a dataset with 95% HRE reports, which initializes the first HRE database in the patient safety community.

**Conclusions:** We proposed a strategy to initialize and grow a database for HREs from FDA reports by retrieving the information from both structured and unstructured fields. This strategy and our HRE database can help fill the void of HIT-related resources and hold promise in aiding the understanding, characterization, discovery, and reporting of HREs toward improved patient safety.

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**202**

**CPRIT Grantee Poster Session B**

**A Model for Emotion-based Visualizations for Conversational Agents in HPV Vaccine Counseling**

**Rebecca Lin, John Hopkins University; M. Amith; C. Tao**

**Introduction:** Patient-centric conversational agents, software systems that dialog with human patients, hold potential in HPV vaccine counseling. Emotions influence perceptions and decisions and are especially strong in healthcare situations. When enabled to express emotions, conversational agents could impact a patient’s willingness to be vaccinated and may improve patient satisfaction. The objective of our study is to create an ontological model that allows emotions to be visualized as colors, shapes, and lines. We can integrate the ontology with patient-facing software tools, like embodied conversation agents, in clinical settings to improve patient-provider interaction.

**Methods:** Using published emotion taxonomies, we matched 25 emotions to a set of visualizations that used colors, shapes, and lines. The visualizations were from a review of published research. We used Stanford’s Protégé ontology authoring tool to create our model, termed the Visualized Emotions Ontology, that aggregated the published taxonomies and the emotion-associated visualizations. Using a scoring metric, we compared our ontology with a set of cognitive-related ontologies to assess domain coverage, readability, and linguistic quality.

**Results:** The final model was published as an ontology with 126 concepts and 11 unique links among the various concepts. For example, a black downward triangle with purple strong lines is emotionally linked to the OCC emotion of fear. In addition, we have aligned the visualizations with each of the 25 emotions. Compared with other cognitive ontologies, our approach is better in terms of readability (0.76 to 12) and domain coverage (0.97, z=0.61), and domain coverage (0.82, z=0.39).

**Conclusions:** We plan to validate and assess the visualizations of emotions by surveying CPRIT fellows in addition to crowd-sourcing through Amazon Mechanical Turk. Also, we plan on developing software that will harness the model to create an interactive expert system that can be used to convey health communication. Acknowledgement: UTHouston Innovation for Cancer Prevention Research Training Program Pre-Doctoral (Cancer Prevention and Research Institute of Texas grant # RP160015).

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**203**

**CPRIT Grantee Poster Session A**

**Targeting the G-Triplex Intermediate in G-Quadruplex Folding for Potential Chemoprevention Applications**

**Sean Harwin; Texas University; H. Bracey; D. Lee; I. Demundo; N. Navipan; K. Tiipaysak; B. Tudosuan; K. Vasquez**

**Introduction:** The mechanisms underlying genetic instabilities that lead to events such as cancer-associated chromosomal deletions, translocations, and rearrangements have yet to be fully clarified, but it has recently been shown that structured DNA (i.e. non-B DNA) often co-localize with hotspots of genetic instability. We hypothesize that the genetic instability associated with non-B DNA-forming sequences is a function of the stability of the non-B DNA structures that enable these forms of cancer. The long loops of these structures will decrease the DNA damage and cancer-associated genomic instability associated with these sequences. **Methods:** Our approach to identify non-B DNA destabilizing ligands exploits recent findings that specific non-B DNA structures (G4-DNA and H-DNA) fold via long-lived (i.e. seconds) intermediates. We propose that ligands that target these intermediates will effectively destabilize these non-B DNA structures by inhibiting their folding. We used CD spectroscopy, UV thermal-difference spectroscopy, and Tm measurements to characterize the topology and thermal stability of the folding intermediates (G-triplex) for a variety of truncated G4-DNA sequences. We also carried out a virtual screen in order to identify ligands that bind to a structurally well-characterized G-triplex, the truncated thrombin-binding aptamer (TBA) G4 DNA. **Results:** G-triplex formation is a general phenomenon for a wide variety of truncated G4-DNA sequences. We detected 25 different variants of the G=1T1+G=1T1+G=1 sequence as well as truncated versions of the TBA and human telomeric G4 DNA in both forward and reverse permutations. All of these sequences can adopt G-triplex structures. However, we note that the number of nucleotides in the loop and palindrome sequence direction affect G-triplex topology. Sequences with longer G-tracks tend to form parallel G-triplex, as do sequences with fewer loop residues. Permutation of the direction of the truncated G4 DNA sequence also affect G-triplex folding topology. Environmental effects on topology were also noted, with divalent metal ions (Mg2+ and Ca2+) favoring parallel topologies. Virtual screening against the antiparallel truncated TBA G-triplex reveals a number of viable ligand binding sites that are predicted to interfere with folding to G4 DNA. **Conclusions:** G-triplex folding intermediates of G4 DNA structures are promising targets for small molecule G4 DNA destabilizing ligands. The effect of the destabilization of G4 DNA on the genetic instability associated with these sequences in human cells will provide crucial evidence for the role of structural stability in genetic instability and potential lead chemopreventive agents.

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**204**

**CPRIT Grantee Poster Session B**

**Preliminary Big Data Textual Analysis of HPV-related Discourse on Reddit**

**Muhammad “Tuan” Amith, The University of Texas Health Science Center at Houston; P. Cuccaro; L. Savas**

**Introduction:** Vaccination against HPV, a known cause of cancer, is lower than projected, and the rate is lower for boys than for girls. Online health information has an impact on individual health efficacy, and through social media, plays an important role in consumer health literacy. To further understand this demographic and their discourse of HPV information, we investigated the use of the social media platform Reddit, skewed toward young, white males, for HPV- and vaccine-related content. To the best of our knowledge, this is the first study to use Reddit to understand HPV-related research and one of a couple for health research.

**Methods:** We utilized big data and natural language processing tools, like MongoDB, Stanford’s Deep Learning for Sentiment Analysis, and custom Java code, to retrieve, analyze, and store data from the Reddit corpus of submissions (n=282,925,243). We queried and analyzed Reddit submissions between 2007 and 2016 based on keywords pertaining to HPV and its vaccine (n=10,205). Using regression analysis, we measured submissions for valence (positive, negative, neutral annotations), character length, and ratings (up and down votes) for their impact on engagement (number of comments to the submission).

**Results:** Most HPV-related submissions to Reddit appeared to have negative or neutral disposition. While valence and character length had no influence on engagement of the HPV-related topic, the increased number of the up votes and the decreased number of the down votes did affect user engagement (p<0.05).

**Conclusions:** We discovered that numbers of up votes associated with a Reddit submission may have an effect on health consumer engagement with an HPV-related topic. This study may help health experts engage a population on social media and stimulate further research to analyze health content from Reddit. Future directions could include applying informatics methods from our previous research, qualitative analysis of the content, and associated comments from the submissions to extrapolate new knowledge from health discourse on Reddit. Acknowledgement: UTHouston Innovation for Cancer Prevention Research Training Program Pre-Doctoral (Cancer Prevention and Research Institute of Texas grant # RP160015).

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Twitter data. Unlike previous efforts primarily focusing on high-level sentiment extraction (i.e., “Positive,” “Negative” and “Neutral”), our system can further identify the exact reasons that caused the negative opinions (i.e., “Safety,” “Efficacy”). Combinations of related keywords were used to collect English language tweets. A gold standard consisting of 6,000 tweets was manually curated. Different machine learning algorithms were compared and the system performance was improved by using hierarchical classification and parameters tuning. 10-fold cross-validation was used to evaluate system performance. We then applied the system on a large-scale Twitter corpus (184,214 tweets, collected from 11/02/2015 to 03/29/2016) and analyze the changes and patterns of different opinions on HPV vaccines. Results: The inter-rater agreement value of the gold standard was high (Kappa=0.851). The hierarchical classification model with optimized parameters increased the micro-averaging F score (harmonic mean of precision and recall) from 0.6732 to 0.7442. 11,778 (60.13%) of the collected tweets were targeting HPV vaccine. Among these tweets, 35,482 (32.0%) tweets were categorized as “Negative”. For the “Negative” tweets, safety concerns take up to 79.2%. We identified a coincidence between real world events and Twitter contents. The trends of different opinions were extracted. The rate of negative information was found much higher on weekends than the middle days of the week. Conclusions: Our system provides us an automatic and efficient way to extract public opinion and understand negative information on HPV vaccine spread on Twitter and provides real-time feedback to the clinical and public health professionals so that they can identify rumors or misfacts on HPV vaccines. Acknowledgement: UTHealth Innovation for Cancer Prevention and Research Training (IPRT) was generously funded by (Cancer Prevention and Research Institute of Texas grant #RP160015). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.
Physician-reported human papillomavirus (HPV) recommendation and initiation among adolescent patients (11-12 years): Does wording matter?

**Methods:** In 2015, we conducted a cross-sectional survey in a large urban Texas pediatric clinic network (51 clinics) to ascertain the method of delivery of HPV vaccination recommendations for patients (11-12 years). Survey data were merged with electronic medical records to ascertain the HPV vaccination initiation status of over 18,000 patients. We used multivariable multilevel generalized linear models clustered by clinic to calculate the adjusted odds ratios controlled for patient and physician demographics. **Results:** A total of 134 pediatricians responded to the survey (60%). After controlling for patient and physician demographics, a bundled, presumptive HPV recommendation was significantly associated with HPV initiation. A recommendation of “Your child is due for two vaccines: Tdap, HPV, and meningococcal vaccine” was significantly associated with an increased odds of HPV vaccination initiation compared with a more ambivalent message of “Your child is due for two vaccines, Tdap and meningococcal. There is also the HPV vaccine, which is optional” (OR: 1.99, 95% CI 1.52-2.60). **Conclusions:** While the CDC identifies providers’ strong recommendations as critical to HPV vaccination initiation, including promoting the bundled approach, to our knowledge, this study is the first to provide strong evidence that bundling the HPV vaccination recommendation increases vaccine uptake. These findings will inform development of HPVcancerFree to increase bundled presumptive HPV vaccination recommendations.

**CPRIT Grantee Poster Session B**

Correlate and patterns of participation in a comprehensive cancer survivorship program among safety-net patients Sandi Pruitt; The University of Texas Southwestern Medical Center; Z. Ge; E. Berry; E. Borton; K. Argenbright; D. Heitjan

**Introduction:** Currently, there is no single, evidence-based standard of care for the provision of diverse comprehensive cancer survivorship services such as nutrition counseling, support groups, and nurse education. Thus, survivors can select among the many services they receive. To increase the evidence base on patterns of participation and factors influencing participation, we studied cancer survivors receiving care at an urban safety-net healthcare system serving low-income, under- and uninsured cancer patients in Tarrant County. **Methods:** We merged data from three sources: survey data from the health system, electronic medical records from the health system, and the Moncrief survivorship program database. We identified patients diagnosed with any cancer type, 2008-2015, using registry data. We compared participants to non-participants by tumor characteristics, diagnosis year, sociodemographic and behavioral factors, and insurance type using logistic regression. We examined characteristics associated with intensity of program participation by negative binomial regression. We identified patterns of utilization by cluster analysis. **Results:** Among 8,325 cancer patients, 467 (5%) enrolled in the survivorship program and completed at least one session. Program participants were largely white (72%) and minorities: Black (32%), Hispanic (38%), and white (28%). Most participants completed at least one nurse visit (76%), whereas fewer completed group nutrition sessions (13%) or individual exercise sessions (5%). Fewer than 4% completed social work visits, support groups, psychotherapy, or individual nutrition counseling. Odds of participation in any program differed (p<0.05) across multiple patient and tumor factors. Briefly, program participants were more likely to be female, younger, and black or Hispanic. Participation also varied by cancer type and diagnosis year. **Conclusions:** Our results provide evidence about patterns of participation in a comprehensive cancer survivorship program among patients of an urban safety-net health system. Findings describe the services survivors seek and receive and barriers that drive their participation. Our research suggests that bundling different services may better meet survivors’ needs and interests. Additional research is needed to understand the impact of survivorship care on healthcare utilization and patient outcomes.

**CPRIT Grantee Poster Session A**

A soft, wireless implantable device for the treatment and prevention of local recurrence by photodynamic therapy in a murin model Sonny Gunadi; Leeds Institute of Biomedical & Clinical Sciences, University of Leeds; D. Jayne; S. Park

**Introduction:** A more recent option for such patients is photodynamic therapy (PDT) which uses a combination of light, oxygen, and a drug known as a photosensitizer. However, the effectiveness has been limited by a number of important factors, the major one being patient compliance, which includes skin reactions due to uptake of the photosensitiser drug by skin cells and requires patients to stay out of sunlight for at least a week after treatment, (ii) an incomplete understanding of the differing response of cancer and normal tissues to photodynamic therapy, and (iii) lack of methods to monitor tumour response and adjust drug dosage accordingly. These factors represent technical challenges that this paper addressed and a proposed system showed the potential for use in research or settings. **Methods:** Repetitive ultra-low-fluence PDT (uPDT) is a novel form of PDT that uses repetitive low light irradiance with the same total photons (PS) doses that are applied over longer periods to ensure treatment completion. Previously, intraoperative PDT has been administered using a single PS dose with intense light irradiance due to the limited surgical window. Consequently, oxygen, which is essential in ROS generation, is not adequately replenished for sustained PDT effect, limiting its efficacy. Our strategy to overcome this limitation is to apply uPDT through a novel implantable device. **Results:**
Current light delivery technologies are largely impractical for preclinical and clinical application. The efficacy of uPDT has been established in studies using glioma spheroids, with an increase of 17 uW/cm² over 24 hours in 3-day cycles with additional PS doses— in comparison, the typical light dose for conventional PDT is about 50 J/cm² at an irradiance of 5-50mW/cm², and clinical PDT uses fluences of 10-100 times magnitude. Our preliminary work using HT-29 CRC cell-line has shown promising results as well. We have successfully achieved critical first steps towards meeting the above technical challenges, and the work demonstrated here would enable the extension of these successes to provide the platform for revolutionary discoveries and therapeutics for the prevention and treatment of local recurrence.

213 Poster Session A Attitudes, Barriers and Knowledge of HPV Vaccination in Health Professional Students

**Introduction:** Significant research has evaluated the attitudes, knowledge and barriers of obtaining HPV vaccination in college students, and a few studies have investigated similar parameters in health professional students; however, most were limited to a single profession and performed outside the United States. It is important to evaluate these factors in health professional students as it may impact their future patient care and delivery of HPV vaccination. The objective of this study is to assess the attitudes, barriers and knowledge of HPV vaccination in health professional students.

**Methods:** This is a cross-sectional study. A survey was offered to every student accessing clinic services. Participation was voluntary and respondents could choose to answer any questions they did not wish to. The clinic takes care of students enrolled in medical, dental, nursing, public health, graduate school, and the school of biomedical informatics in a health university.

**Results:** A total of 266 surveys were collected during the initial collection phase of 4 months. The majority of students who completed the survey were in health professional programs and these patients experience poorer outcomes. Individuals

214 Poster Session B Stakeholder engagement to initiate lung cancer screening in an urban safety-net health system

**Introduction:** Although several reports have demonstrated successful lung cancer screening programs, even those in community settings have focused largely on insured populations. There is little guidance describing how best to implement computed tomography (CT) based screening in settings that care for minority, underserved, and other medically-underserved populations that face highest risk of and worst outcomes from lung cancer. While these patients stand to benefit most medically-underserved populations that face highest risk of and worst outcomes from lung cancer. While these patients stand to benefit most from guideline-based screening, they may also be those least likely to comply with the cancer screening process. From our experiences and in relevant literature, we developed a stakeholder engagement plan to identify and address logistical challenges to implementing CT-based screening as clinical standard of care in an urban, integrated safety-net health system.

**Methods:** Parkland Health & Hospital system provides care for uninsured patients through a combination of federal, state, and county-supported programs for more than one million under- and uninsured residents (39.5% Hispanic, 34.4% Non-Hispanic White, and 20.8% African American) of Dallas County, Texas. Over a 14-month period (February 2016-April 2017), our program team worked closely with a range of institutional stakeholders. We presented to patient and caregivers drawn from the community to solicit patient-level guidance regarding barriers and facilitators to completing the screening process, including knowledge and perceptions. We engaged multiple institutional stakeholders (including providers, patient navigators, radiologists, pulmonary medicine physicians, and smoking cessation personnel) to develop a health system process for guideline-based referral, initial CT screening, results reporting and clinical follow-up.

**Results:** Through an iterative process based on patient and stakeholder feedback, we developed an EHR-based order designed to (1) capture demographic data relevant to screening eligibility, (2) provide CMS-mandated documentation of patient counseling, and (3) deploy Lung-RADS standardized reporting to minimize additional workload on referring clinicians. Employing available population data from earlier screening programs and research studies— including smoking profiles and sociodemographic characteristics—we organized an in-service campaign to inform primary care sites of order availability. As the campaign proceeded, we reviewed patient volumes, process performance, clinician and patient feedback to inform screening program development and adaptation to our system setting.

**Conclusions:** Medically underserved populations face the highest risk of and worst outcomes from lung cancer. Health systems seeking to implement lung cancer screening programs should employ robust patient and stakeholder engagement plans to optimize patient and provider uptake of evidence-based screening.

215 Poster Session A Soft tissue microstructure evaluation using high frequency ultrasound

**Introduction:** Breast-conserving therapy (BCT) when compared with the traditional mastectomy, BCT has been shown to be an excellent method for treating cancer. Composed of a lumpectomy and radiation treatments, the success of BCT depends heavily on the outcome of the lumpectomy. The success of the procedure, in which the tumor along with a small margin of healthy tissue is removed, is determined by the presence or absence of malignant cancer cells in the surrounding tissue. Medical students, female, aged 18-26 years, and Caucasian. The majority (96%) of the respondents know about the HPV vaccine. Interestingly, 58% of respondents had not received or completed a 3-dose series; of those who hadn’t initiated vaccination, 64% did not wish to, while 68% of incompletely-vaccinated respondents were not interested in completing the series. ‘I’ve only been with 1 partner and have low risk of acquiring the infection was the most common reason cited. When looking at knowledge of cancers caused by HPV, students in medical school knew the most.

**Methods:** Our study focused on the ultrasound measurement peak density. This parameter studies the material’s frequency to the applied ultrasonic pulse. We investigated peak density through experimental, computational, and analytical means in order to understand how the material properties affect the ultrasound measurement. Tissue-like phantoms featuring varying sizes and concentrations of glass microspheres were measured for peak density using 31.5 MHz ultrasound transducers. Finite element analysis using COMSOL modeled the acoustical response of a system of glass scatterers. These simulated results were then compared with experimental data. Results from students at The University of Texas.

**Results:** The phantom experiments showed peak density to vary with both the size and concentration of the scatterers present. Simulations showed similar trends to the phantom experiments. Analytical scattering cross-sections, which consider the total amount of scattering present in the system, were calculated. These cross-sections were found to behave analogously to the peak density results suggesting a relation to the materials’ scattering properties. Expanded simulations using different materials showed peak density to change with the scatterers’ material properties as well. These values were also compared with the scattering cross-sections and showed similar behavior further implying the relation between peak density and scattering. **Conclusion:** From our experiments and simulations it was observed that the ultrasonic parameter of peak density was responsive to changes in the microstructural environment. These values were also compared with the scattering cross-sections and showed similar behavior further implying the relation between peak density and scattering. **Conclusion:** From our experiments and simulations it was observed that the ultrasonic parameter of peak density was responsive to changes in the microstructural environment. These values were also compared with the scattering cross-sections and showed similar behavior further implying the relation between peak density and scattering. **Conclusion:** From our experiments and simulations it was observed that the ultrasonic parameter of peak density was responsive to changes in the microstructural environment. These values were also compared with the scattering cross-sections and showed similar behavior further implying the relation between peak density and scattering. **Conclusion:** From our experiments and simulations it was observed that the ultrasonic parameter of peak density was responsive to changes in the microstructural environment. These values were also compared with the scattering cross-sections and showed similar behavior further implying the relation between peak density and scattering.
at higher skin cancer risk are advised to practice sun protection, undergo full-body physician skin examination (PSE) and conduct skin self-examination (SSE). It is also known that these risk reduction practices in patients with CLL. We evaluated sunscreen, sun protection, skin examination practices and relevant correlates in patients with CLL. 

**Methods:** Eligible patients were diagnosed with CLL, aged ≥18 years and fluent in English. Patients (n=100) attending the outpatient leukemia clinic were interviewed by a research nurse during a survey covering sun protection and skin examination practices. **Results:** Most patients were male (62.2%), non-Hispanic white (88.5%), married (80.4%) and had completed college/graduate school (62.3%). Average age was 64.7 (SD=10.7, range=37-87) years. Skin cancer personal history was reported by 36.8%. Almost one-third (29.6%) reported one or more sunburns during the past year. Most reported routinely wearing sunglasses (68.0%) and sleeved shirts (81.0%); fewer routinely used sunscreen (42.0%), reapplied sunscreen (19.6%), used SPF lip balm (25.0%), wore a wide-brimmed hat (31.0%) or stayed in the shade (35.4%). Overall, patients “sometimes” practiced sun protection (M=3.34, SD=1.5-1.5 “never” to “always” scale). Most (70.0%) reported having had a PSE; 51.0% in the past year. Some (22.2%) reported SSE in the past 3 months. In multivariable analyses, significant sunburn correlates included younger age (p<.01), male sex (p<.05) and having had skin cancer (p<.01). Patients were more likely to conduct SSE if they had been shown how to perform SSE (p<.01) and reported greater confidence in performing SSE (p<.05). The odds of having had the PSE also increased with patients’ SSE confidence (p<.01). Willingness to prepare for sun protection was positively associated with practice of sun protection (p<.001). Some patients reported a significant sunburn history, SSE and use of sunscreen, wide-brimmed hats and shade was relatively infrequent. Most reported having a PSE; some had not had one recently. To our knowledge, this is the first study of sun protection and skin examination correlates in patients with CLL, a population at increased skin cancer risk and health venue affiliation networks and HIV risk and prevention among young MSM. Subjects were recruited into YMAP, using Respondent-driven sampling (RDS) to reach this “hard-to-reach” problem. The validity of estimating disease prevalence using RDS relies heavily on the accuracy in measuring the number of contacts or peers a respondent has (network degree). However, in practice, this measure is often problematic because it is self-reported. **Methods:** We propose a new statistical approach to adjust self-reported network degree by using information of YMSM’s venue attendance to better approximate the network degree. The new venue-based degree measure can be used for RDS estimators. Our new method yields a higher efficiency (smaller variance) and less bias. The rationale supporting this approach is that peer referral is likely to occur when young MSM meet sex partners at social and public cruising venues, i.e., MSM with more frequent venue attendance tend to meet and have more social contacts, and thus have a higher degree of peer recruitment. **Results:** Our method tended to have narrower CIs compared to the self-reported degrees for HIV estimates. Our simulation study to assess validity also showed that proposed method yields less biased estimates than the standard one. **Conclusions:** YMSM represent a population most at risk of new HIV diagnoses, developing novel approaches that can inform cost and intervention strategies are critical as we move toward HIV elimination and cancer prevention in U.S. This work was supported by the National Institutes of Health (1R01MH100021, 1R01DA039934, and 1R21GM113694). Ming is supported by UTHSC Health Innovation for Cancer Prevention Research Training Program Pre-doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP160015). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.
sessions showed the need for recruiters to improve their rate of speech, eye contact, and body posturing. Verbal communication barriers included language incompatibilities between recruiter and potential donor including, recruiters’ use of jargon, and their inability to adapt information to differing cultural norms. **Conclusions:** Recruiters require training focused on improving mistrust and misinformation using effective verbal and nonverbal messages. The training should include nonverbal communication modules focused on overcoming barriers and kinesthetic and verbal communication modules focused on adapting and perception checking.

**Poster Session B:**

**A Prospective Investigation of the Effects of Pre-cessation Reduction of Anxiety Sensitivity and Dysphoria on Withdrawal in a Tobacco-Use Treatment Trial**

**Alicia Lopez, University of Houston; J. Bakhshiae; A. Ruiz; K. Manning; L. Garey; N. Mayorga; P. Kulesz; M. Zvolensky**

**Introduction:** Prevailing theory and research suggests the psychological and physiological discomfort associated with tobacco withdrawal may play a formative role in the risk of cessation failure. Yet, research elucidating effective vulnerability characteristics that contribute to increased tobacco withdrawal severity during periods of planned abstention is highly limited. In the current study, we explored whether smokers with greater reductions of Anxiety Sensitivity (AS) and dysphoria during a smoking cessation intervention would experience less severe post-quit tobacco withdrawal. **Methods:** The interactive effect of change (pre-intervention baseline to quit-day) in AS and dysphoria in relation to post-quit withdrawal severity (quit-day through 12-week post-quit) was examined among treatment seeking adult smokers enrolled in a smoking cessation trial (n = 199; 55.3% female; 58% Baseline; SD = 14.0). **Results:** Results indicated that the interactive effect of change in AS and dysphoria was related to linear change in post-quit withdrawal symptoms. Specifically, larger reductions in AS were associated with a faster decline in the severity of withdrawal symptoms across the 12-week post-quit period only for individuals with lower (but not higher) reductions in dysphoria. **Conclusions:** The findings indicated that reducing levels of AS and dysphoria pre-quit is broadly related to the degree of change in post-quit withdrawal symptoms. Collectively, these data suggest there is apt to be clinical merit to employing strategies to address AS and dysphoria pre-quit that could actively manage emergent withdrawal symptoms following smoking cessation treatment. Keywords: Anxiety sensitivity, dysphoria, smoking cessation, tobacco withdrawal

**Poster Session A:**

**A Bayesian Framework for Evaluating Leukemia Risk From Electronic Health Records**

**Ahmed Al Kawam, Texas A&M University; A. Sen; A. Datta**

**Introduction:** Cancer risk assessment (CRA) models are considered an efficient tool for identifying high-risk individuals. CRA models have an important role in cancer prevention and early detection by promoting a cost-effective distribution of finite resources, such as cancer screening tests. However, these models can have two main limitations: (1) they are often presented in the form of questionnaires, which limits their automated application to large-scale medical data and (2) they are generally static and cannot easily be adapted to account for the differences between local populations across counties, states, and countries. **Methods:** To overcome these challenges, we utilize Electronic Health Records (EHR) available in most areas in the US. EHRs are composed of patient and clinical information routinely collected at each healthcare visit. We use diagnosis codes stored in the EHR data to identify a list of risk factors associated with leukemia. Furthermore, we develop a Bayesian framework for adaptive risk assessment. The Bayesian framework utilizes prior information and available data to perform accurate risk assessment. The developed model adapts to the existing data and can be updated as more data becomes available. We apply our method to EHR data collected at the University of Texas at Austin's Deaconess Medical Center between 2001 and 2012. Our model includes three steps: (i) prior information is incorporated into the Bayesian model in the form of a probability distribution for the different risk factors of leukemia; (ii) the prior is combined with a likelihood function to produce a posterior distribution of coefficient values; and, lastly, (iii) simulations are drawn from the posterior distribution to create an empirical distribution for the population using a generalized linear model. **Results:** Our method was able to detect a clear separation between the leukemia subjects and the controls. We tested the significance of this separation and achieved a p-value less than 1.0e-12. According to this risk score distribution, 52% of the leukemia subjects were assigned an average cancer risk score. Furthermore, most of the identified diagnosis codes found were tightly linked to leukemia. **Conclusions:** Using EHR data and a Bayesian framework, we have developed an effective leukemia CRA model that overcomes the challenges of traditional CRA methods.

**Poster Session B:**

**Ecological comparisons of inter-regional and temporal variations in sex-ratios of age-standardized cancer incidence rates**

**Syed-Mayorga; P. Datta; J. Zvolensky; M. Bakhshaie; A. Ruiz; K. Manning**

**Introduction:** Comparisons of cancer incidence rates from international cancer registries are valid if ascertainment of cases approaches 100%. Sex ratio (SR) analysis of cancer incidence (age-standardized incidence rates in males relative to females) mitigates some of methodological challenges caused by inter-registry differences. We present an analysis based on European and North American cancer registries. The study presents SR as a useful and robust measure of cancer occurrence, to infer on causes through worldwide comparisons. **Methods:** Cancer Incidence in Five Continents (CI-5) from International Agency for Research on Cancer was used to access incidence data on 30 different cancers in 3 time-periods (i.e., 1974-77; 1988-92 and 2003-07) for 23,154 and 281 cancer registries. Descriptive methods were used with recourse to mixed-effect regression. **Results:** Cancer types with consistently high variation of SR (SRV) over time were lung, bladder, esophagus, larynx, and oral-cavity. Cancers with consistently low SRV time were colon, Hodgkin’s and non-Hodgkin’s lymphoma, leukemia, thyroid, gallbladder and skin melanoma. In 1973-77, highest SR were observed for following cancers: larynx (112.0 in Doubs, France) followed by lip (59.0 in Zaragoza, Spain), pharynx (31.0 in Doubs, France), tongue (30.0 in Slovenia), esophagus (21.3 in Bas Rhin, France), mouth (15.5 in Slovenia), lung (15.1 in Bas Rhin, France), and kidney (11.6 in Doubs, France). The lowest SR was noted in Warsaw, Poland for thyroid cancer (0.1). Compared to 1973-77, SR of Hodgkin’s lymphoma was high in both 1988-92 and 2003-07 (9.0 in Lima-Pera and Karunagappally-India versus 3.5 in South Australia). In mixed-effect analysis with 76 registries from 1983 to 2007, cancer of the pharynx (in age category ≥20) represented highest SRV and lowest for cancer of thyroid (0.54). The highest inter-regional variation in SR was observed for larynx and lung and the lowest for thyroid cancer. **Conclusions:** A change in the SR over time for some cancers indicates a role of environmental factors. However, some of the unexplained sex differences are unlikely to be explained by environmental factors and it is plausible that there is a significant role of intrinsic sex-specific factors that modify the effect of environmental causes. The patterns of incidence rates based on SR supports that environmental, genetic and lifestyle factors, and even random error in cell replication can influence individual risk. From a prevention perspective, understanding the gender-disparities (in terms of socio-cultural context) in cancer registration is critical to public health practitioners.
**Introduction:** Cognitive problems following cancer diagnosis and treatment are among the most difficult side effects to deal with. Moreover, many cancer survivors find that their financial situation is worse, and they lack the ability to cope with their concerns or suggest ways to address the problems. 

**Methods:** Twenty women from a community oncology practice and cancer resource center were recruited to participate in a 6-week group intervention to build cognitive abilities. Consistent with Social Cognitive Theory, the intervention focused on enhancing voluntary strategies, as well as discussions about other factors identified from previous literature to affect cognitive abilities, such as fatigue, insomnia, physical inactivity, and emotional distress. In addition, women were assigned specific cognitive exercises from a commercially available brain training program and asked to practice 45 minutes for 3-4 times a week. Women served as their own controls. Outcome measures consisted of performance on well-established neurocognitive tests and self-reported measures of cognitive concerns, emotional distress, fatigue, sleep disturbances, memory and cognitive strategies, and health-related quality of life. Participants were tested twice prior to the intervention to control for testing effects and to investigate naturally occurring changes over time in outcome measures before exposure to the intervention. 

**Results:** Women had an average age of 53 years; most were employed and well educated. Half had been diagnosed within the past two years, and nine were taking endocrine therapy. Eighteen of the 20 participants completed the study, and two-thirds of the women attended at least 5 of the six classes. Scores on neuropsychological tests did not increase from immediately prior to the intervention to post-test, but scores on PROMIS measures of cognitive concerns, emotional distress, and fatigue decreased significantly following participation in the intervention. Reported use of cognitive strategies also increased significantly. 

**Conclusions:** This exploratory study demonstrated the feasibility of combining a health promotion intervention designed to build cognitive abilities coupled with brain training homework. At the post-intervention debriefing session, participants emphasized that the interaction with the facilitator was an important motivator for behavioral change in this area. While results should be interpreted cautiously because of the small sample size and lack of a control group, these findings add to the growing body of evidence supporting the efficacy of cognitive interventions to help survivors address their cognitive concerns. Funded by the Shivers Foundation.

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**Abraham J. Yee, The University of Texas M.D. Anderson Cancer Center**

**Poster Session A**

**Clinical factors affect long-term survival of advanced hepatocellular carcinoma patients**

**Melissa K. Ok, The University of Texas M.D. Anderson Cancer Center**

**J. David Davis, D. R. Hlia, M. Akce, M. Uemura, A. Kaseb, S. Chang, M. Hassan**

**Introduction:** Most hepatocellular carcinoma (HCC) patients are diagnosed at late stages, and the 5-year relative survival rate for patients with advanced HCC is only 3%. Many factors – demographic, clinical, and other – affect survival of patients with advanced HCC. A recent study using the Surveillance, Epidemiology, and End Results (SEER) data found that a small proportion (10%) of patients diagnosed with advanced HCC survived longer than 12 months. Notably, longer survival was correlated with age, female sex, year of diagnosis, tumor grade, and surgery status. The aim of this study was to explore additional clinical factors associated with longer survival in advanced HCC, such as smoking history and presence of other diseases. 

**Methods:** To analyze additional characteristics not examined in the SEER data, we identified 249 individuals with Stage IVA and IVB HCC from patients who participated in a University of Texas MD Anderson Cancer Center clinical-epidemiological study from 2000-2014. We used the median overall survival of patients who received systemic therapy (5.8 months) to stratify patients into two groups: long-term survivors (survival > 5.8 months) and short-term survivors (survival ≤ 5.8 months). Using data from personal interviews and medical records, we compared the two groups by clinical, demographic, and other factors. Variables that differed significantly between the two groups were included in a multivariate Cox proportional hazards model used to identify independent predictors of prolonged survival among patients diagnosed with late-stage HCC. 

**Results:** Clinical features of long-term survivors differed significantly from those of short-term survivors while demographic and other factors, such as age and hepatitis virus status, did not differ between the two groups. Cox model analysis indicated that clinical factors, such as absence of cirrhosis and better Child-Pugh scores, were independent predictors of prolonged survival. 

**Conclusions:** Clinical characteristics of HCC patients diagnosed with advanced disease rather than prolonged survival. Further better management of liver disease may help improve survival from HCC, and understanding the mechanism of this benefit is worthy of further inquiry.

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**Abigail E. Williams, The University of Texas M.D. Anderson Cancer Center**

**Poster Session A**

**Implementation costs of a multi-component intervention to increase human papillomavirus (HPV) vaccination in a network of pediatric clinics**

**Jarrod Eska, The University of Texas Health Science Center at Houston**

**D. Larsson, L. Savas, R. Shegog, C. Healey, S. Spinner,**

**M. Fernandez; S. Vernon**

**Introduction:** HPV vaccination is both a clinically and cost-effective way to prevent HPV-related cancers of the cervix, oropharynx, and others. Increased focus on HPV-related cancers has motivated development of intervention strategies to increase vaccination rates of young adolescents to realize Healthy People 2020 national goals. As providers and healthcare organizations consider vaccination initiatives, it is important for decision makers to understand the resources associated with implementing these strategies. This paper assessed the implementation costs of an evidence-based multi-component intervention in a large network of pediatric clinics. 

**Methods:** Healthcare provider assessment and feedback, reminders, and education; and parent education/reminder strategies were implemented in a network of 51 pediatric clinics to improve the HPV vaccination rate. A micro-costing method was used to prospectively estimate program costs. Project and clinic staff logs, system-generated reports, and vendor contracts were used to measure personnel time and material costs. A sensitivity analysis assessed the effects of uncertain and variable cost factors. 

**Results:** Implementation costs of the four intervention strategies totaled $134,999. The $97,228 in fixed costs included contracted services from third-party vendors to implement automated electronic health record vaccination reminders for providers and parents and to introduce a network-tailored mobile application to educate parents on HPV and HPV vaccination. Variable costs, totaling $69,335, include staff time, supplies, and training necessary to implement each intervention strategy. Assessment and feedback was implemented at an average cost of $672 per clinic. The provider education and provider reminders increased the average cost to $930 and $1,762 per clinic, respectively. The parent component increased total average cost of implementation per clinic to $2,845. Including an additional ten clinics reduced the total average cost per clinic to $2,532 with an average reduction of $31 for each additional clinic. 

**Conclusions:** Fixed costs represented the largest share of the four-programs intervention strategy, including additional clinics reduced the total average cost per clinic, however, only by a fraction of the total program implementation cost. This analysis serves to inform decision makers on the costs of implementing a multi-component intervention to increase HPV vaccine uptake. Additional research is required to assess the effectiveness and the cost-effectiveness of each strategy in achieving the goal of higher immunization rates.

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**Abigail E. Williams, The University of Texas Southwestern Medical Center**

**Poster Session A**

**Imaging glucose-stimulated zinc secretion from the prostate by MRI for the detection of prostate cancer lesions**

**Veronica Clavijo Jordan, The University of Texas Southwestern Medical Center**

**J. Li, D. Yang, L. Liu, R. Halia, A. Abdel-Wahab; M. Akce; M. Uemura; A. Kaseb; S. Chang; M. Hassan**

**Introduction:** Zinc (II) is essential in the correct function of secretory organs like the pancreas, and prostate. It is known that total zinc(II) concentrations in the prostate are the highest in the body (1-10 mM), and also that those levels are decreased in prostate cancer, while remaining unchanged in the prostate with benign conditions. Here we report the use of a Gd-based zinc(II) sensor to distinguish prostate cancer from healthy tissue in a transgenic adenocarcinoma of the mouse prostate model (TRAMP) in vivo with MRI and the validation of glucose-stimulated zinc secretion from prostate glands with Synchrotron Radiation- X-Ray Fluorescence (SR-XRF). 

**Methods:** 9 C57Bl6 healthy and 10 TRAMP mice were imaged 10 minutes, the prostates were immediately resected and frozen. 50 um-thick sections were scanned using SRXRF and Zn, Gd, Fe, Cu, and P maps were generated. The concentration values obtained were evaluated for statistical significance by one-way ANOVA. 

**Results:** Given that the mechanism of glucose-stimulated zinc secretion (GSZS) MRI relies on the effective release of Zn(II) into the Gd-laden extracellular space and also on the availability of Zn(II), we evaluated the distribution of zinc, and gadolinium within the gland after a GSZS experiment in order to elucidate the nature of MRI-identified malignant lesions. We found that there is no statistically significant difference in Gd distribution in the gland as a result of either disease or treatment with D-Glucose. Additionally, Zn(II) loss was only found in the lateral lobe of the prostate of TRAMP mice and with high-resolution SR-XRF we found that effective movement of zinc pools from the luminal acinar gland into the basal cells and extra-glandular space of the prostate secreting glands. A combination of zinc content and metal movement sensitivity to glucose were evaluated and found to be decreased with statistical significance during the progression of prostate cancer in TRAMP mice. 

**Conclusions:** These results indicate that GSZS MRI as a technique to detect prostate cancer malignant lesions is multi-factorial comprising of the loss of zinc content, Gd-based zinc sensor distribution, and also on the secretory capacity of prostatic secreting cells. Elucidating the interplay between these factors in the transport and zinc homeostasis could prove valuable in understanding the underpinnings of prostate cancer onset and progression.
Colorectal cancer screening among urban safety-net patients: Using longitudinal electronic health records to measure multilevel social disadvantage. Amy Hughes, The University of Texas Southwestern Medical Center; J. Tiro; B. Balasubramanian; C. Sugg Skinner; S. Pruitt

Introduction: Social disadvantage significantly predicts CRC screening, incidence, stage at diagnosis, and survival across populations and places. Social disadvantage is part of meaningful use electronic health records (EHR) requirements. EHRs can be linked to other sources to create measures of social disadvantage at multiple levels. In our study, we aim to: (1) demonstrate novel measures of social disadvantage through linking patient residential address in EMRs with secondary geospatial datasets; and (2) investigate associations between measures of social disadvantage and CRC screening while controlling for healthcare utilization. Methods: We geocoded longitudinal EHR data and linked them with cadastral and Census data to generate measures of social disadvantage at multiple levels. We assessed heterogeneity of social disadvantage measures. We employed unadjusted and adjusted multilevel logistic regression models to assess associations. Results: We identified 32,965 CRC screening-eligible patients from an existing cohort study within an urban safety-net healthcare system. We used the EHR to assess one-time receipt of CRC screening, via colonoscopy or FIT, in the 18 months following patient enrollment in the existing cohort study. For our safety-net population, neighborhood-level variance and variance in social disadvantage measures was extremely low. In fully-adjusted logistic regression models, measures of patient-level disadvantage and healthcare utilization were associated with CRC screening receipt, but measures of patient-level housing disadvantage and neighborhood-level physical and social disadvantage were not. Conclusions: EHRs offer a plethora of data, and linking these data with secondary datasets can enable creation of longitudinal, multi-sector measurements of social disadvantage. More research is needed to apply these methods and measures to EHR data from more heterogeneous patient populations.

Nonsteroidal anti-inflammatory drug use, obesity and survival from colorectal cancer. Janelle Chavez, The University of Texas M.D. Anderson Cancer Center; J. Davis; Y. San Miguel; M. Overman; Z. Jiang; S. Manuel; S. Kopetz; S. Chang

Introduction: Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with decreased risk of developing colorectal cancer (CRC), and emerging evidence suggests improved overall survival for a subset of patients who regularly use NSAIDs following diagnosis. Conversely, obesity is a known CRC risk factor, however due to mixed findings in the literature, its impact on survival is unclear. The effect of regular NSAID use on CRC survival in the context of obesity is largely unknown. Due to potentially adverse side effects of regular NSAID use, such as gastrointestinal bleeding, it is critical to determine which patients, if any, may benefit from regular use of these drugs after diagnosis. The purpose of this project is to analyze the influence of pre-diagnostic obesity with and without post-diagnostic NSAID use on overall survival in CRC patients. Methods: Patients participating in the Assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) protocol at MD Anderson were invited to complete an environmental survey that includes data on NSAID use and self-reported weight history. These data were combined with information from the medical record to describe recent and ongoing NSAID use. Patients are followed-up for disease and survival outcomes through contact with study personnel and periodic letters from the institution. Survival was compared by obese vs non-obese and NSAID users vs nonusers. Results were adjusted for gender, race/ethnicity, and stage at diagnosis using Cox Proportional Hazards models and adjusted survival curves were generated using the ‘DIRECTADJ’ option in SAS (v9.4). Results: Obesity (BMI ≥ 30 kg/m²) was associated with worse overall survival compared to normal weight. HR = 1.45 (95% CI 1.10 – 1.90 P = 0.02). NSAID use was significantly linked to improved overall survival, HR = 0.81 (95% CI 0.67 – 0.98; P = 0.03). However, when stratified by BMI category, the protective effects of NSAIDs were only evident in the patients with a BMI of ≤ 25 kg/m². HR = 0.75 (95% CI 0.60 – 0.94; P = 0.04). Conclusions: Among colorectal cancer patients, obesity bodes a worse prognosis while NSAID use significantly improves overall survival, but only in patients of BMI ≤ 25 kg/m². These results may help further understand how modifiable CRC risk factors could also impact survivorship. Furthermore, identifying subsets of patients who are most likely to benefit from post-diagnostic NSAID use is an important step toward minimizing toxicities through individualized recommendations, potentially improving treatment and survivorship for colorectal cancer patients.
**ABSTRACTS**

Future in vivo studies. In vitro ADME studies are currently underway. Lead compounds identified also possess favorable physical chemical properties which should deliver good solubility and ADME properties for the identification of multiple lead compounds possessing potent EYA2 inhibition of EYA2 activity. Target specificity of lead compounds was tested using EYA2 CRISPR knockout in cultured cells. New lead EYA2 inhibitors of varying potencies (IC50 ≤ 36-ER-beta in vitro and in vivo). EYA2 is known oncogene in ovarian and breast cancers. The central hypothesis that pharmacological targeting of the oncoprotein EYA2 with small molecule inhibitors can effectively inhibit breast cancer cell proliferation and tumor-initiating function. Methods: Screening assays have been developed to assess and characterize small molecule inhibitors of EYA2, including a standard MTT assays, tumorsphere assay, as well as a recombinant EYA2 phosphatase binding assay. The EYA2 high throughput screening (HTS) assays developed used fluorescence and absorbance-based assays based on OMFP hydrolysis and molybdate green absorbance as readouts. Small molecule libraries were optimized using SAR and existing X-ray structural and modeling data on known EYA2 inhibitors to design and synthesize novel EYA2 targeting compounds. Compound design cycles incorporated “drug-like” physical chemical property parameters such as MW, LogP, tPSA and pKa. Cytotoxicity of drug leads was determined using 3-(4,5 dimethylthiazol-2-yl)-2,5-phenyltetrazolium bromide (MTT) assays as well as in tumorsphere results: This poster will highlight our collaborative program results, wherein more than 430 analogs from different chemical series were designed, synthesized and screened. Efficient synthesis strategies were developed and automated to support our screening programs in vitro studies. Using the fluorescence-based OMFP EYA2 phosphatase and MTT assays, new lead EYA2 inhibitors of varying potencies (IC50 2-50μM) were identified. Structure-activity relationship studies across these chemical series suggested specific structural requirements for inhibition of EYA2 activity. Target specificity of lead compounds was tested using EYA2 CRISPR knockout in cultured cells. Conclusions: To date, >430 analogs from different chemical series for the EYA2 program have been designed, synthesized and screened, which has resulted in the identification of novel small molecule lead compounds for EYA2 inhibition and activity in the MTT cell proliferation and tumorsphere assays. Lead compounds identified also possess favorable physical chemical properties which should deliver good solubility and ADME properties for future in vivo studies. In vitro ADME studies are currently underway.

**231**

CRPRIT Grantee Poster Session B

**Predicting binding modes of peptide-HLA complexes with molecular docking**

Didier Devaurs, Rice University; G. Lizee; L. Kavraki

**Introduction:** Immunotherapy is an innovative cancer treatment that has shown promising results, inducing dramatic tumor regression in numerous patients, across many cancer types. It leverages the immune system to eliminate tumor cells, through cancer vaccines or cell therapies. Since every cell presents at its surface numerous peptides, a patient’s immune system can be “trained” to identify tumor cells by recognizing specific tumor-derived peptides. Peptides are presented by human leukocyte antigen (HLA) proteins that bind them; these peptide-HLA complexes can then be recognized by white blood cells that eliminate diseased cells. What hinders the implementation of this defense mechanism for immunotherapy is that every patient presents a unique set of tumor-derived peptides and requires a personalized treatment. The problem resides in determining which peptides activate specific immune targets for immunotherapy, ranging from thousands of tumor-derived peptides presented by a patient and identified by experimental techniques. Because of such prohibitive numbers, selecting target peptides cannot be done experimentally and has traditionally relied on computational methods that can predict how strongly peptides bind to HLA proteins. Most methods for HLA-binding prediction involve looking for similarities between sequences of candidate peptides and available datasets containing reported sequences of experimentally-identified HLA-binders. However, due to dataset biases, these methods can fail to identify actual HLA-binding peptides. To address this issue, we aim to develop structure-based computational methods to complement sequence-based methods and improve HLA-binding prediction, by analyzing the three-dimensional structure of peptide-HLA complexes using molecular docking techniques. Methods: Protein-ligand docking consists of computationally predicting possible binding modes between ligands and protein receptors. Since most docking tools can handle only small drug-like molecules and not large ligands, such as peptides, we are currently developing a novel docking tool, called DINC, using an innovative incremental protocol. DINC will be used to model peptide-HLA complexes of interest and identify possible HLA-binding peptides. This project will consist of synthesizing DINC to account for receptor flexibility. Results: We will evaluate this enhanced version of DINC by trying to replicate structures of peptide-HLA complexes reported in the protein data bank and to achieve consistency with HLA-binding experimental data. Conclusions: The expected outcome of this project is a new molecular docking tool complementing traditional sequence-based methods to predict target peptides for cancer immunotherapy.

**232**

CRPRIT Grantee Poster Session A

**The University of Texas M.D. Anderson Cancer Center; R. DePinho; J. Baddour; F. Muller; C. Wu; H. Wang; L. Zan; A. Chen; T. Gutschner; Y. Kang; J. Fleming; N. Satani; D. Zhao; A. Achreja; L. Yang; J. Lee; Q. Chang; G. Genevseae; A. Viale; H. Ying; G. Draetta; A. Maitra; Y. Wang; D. Nagrath**

**Introduction:** Cancer genomes possess many deletion events targeting tumor suppressor genes (TSG) and neighboring genes in these loci. These deletion patterns prompted us to consider a systematic approach, termed “collateral lethality,” designed to identify cancer-specific vulnerabilities resulting from the deletion of neighboring genes. These bystanding genes do not appear to be involved in cancer progression, yet encode cell-essential functions and are members of multi-gene families that are functionally redundant and co-expressed. Homozygous deletion of SMAD4 is a frequent event in pancreatic cancer and other cancer types, totaling ~20,000 US cases annually. Treatment of SMAD4-null co-deletion of the neighboring mitochondrial malic enzyme 2 (ME2) gene. In mammalian cells, two genes (ME2 and ME3) encode redundant cell-essential mitochondrial ME activity. Together, ME2 and ME3 function to generate pyruvate to fuel the TCA cycle, and NADPH to maintain ROS homeostasis. These observations prompted our hypothesis that genetic or pharmacological extinction of ME3 activity in a ME2 null cell would specifically compromise cancer cells yet be tolerated in normal host cells possessing ME2 activity. Methods: Inducible shRNA strategies were employed to genetically deplete ME3 in ME2-null versus ME2-intact cells followed by apoptosis measurements, integrated metabolomics, and molecular investigations. Results: Genetic depletion of ME3 in ME2-null, but not ME2-intact, cells resulted in apoptosis and blocked tumorigenic potential. Mechanistically, integrated metabolomic and molecular investigation of mitochondrial ME-deficient cells revealed diminished NADPH production and consequent high AMPK activity, which activates AMP-activated protein kinase (AMPK) and in turn directly suppresses sterol regulatory element-binding protein 1 (SREBP)-1-directed transcription of its direct targets including the BCAAT2 (Branch chain amino acid transaminase 2) gene. We also determined that mitochondrial MEs regulate the utilization of branched chain amino acid (BCAAs), which are transaminase required for BCAAT2 catabolism. BCAA is critical for PDAC tumor progression, and inhibition of BCAAT2 leads to a decrease in the availability of nitrogen pool required for de novo nucleotide biosynthesis. Notably, enforced expression of BCAAT2 can restore tumorigenic potential of ME2 deficient and free nucleotides can restore proliferation in cell culture. Conclusions: Thus, a key mechanism driving cancer cell lethality involves BCAAs as crucial metabolites under the critical regulation of the mitochondrial MEs. These studies reveal a collateral lethal vulnerability in pancreas and other cancers that can be targeted pharmacologically in genotype-defined patient populations. We propose that highly specific ME3 inhibitors could provide an effective therapy across a substantial number of cancer patients.

**233**

CRPRIT Grantee Poster Session B

**Thomas Bartosh, Texas A&M University System Health Science Center; M. Ullian; J. Beaver; H. Nerber; B. Clough**

**Introduction:** Gene-directed enzyme/prodrug therapy (GDEPT), also known as suicide gene therapy, shows considerable potential as a targeted cancer treatment platform. However, routine application in patients remains overshadowed by challenges associated with fabrication of highly efficient transgene/enzyme vectors. Extracellular vesicles (EVs), natural membrane-bound conveyors of bio-molecular information (nucleic acids, proteins, bioactive lipids), have emerged as promising enzyme/drug delivery vehicles. However, no study has exploited the unique ability of apoptotic cell-derived vesicles, known as apoptotic bodies (ABs), to dump their molecular cargo willingly into genetically unstable cells, a hallmark feature of cancer. Thus, in this study we assessed the applicability of ABs in suicide gene therapy. Methods: Genetically engineered ABs were generated from tumor-tropic IPS cell-derived mesenchymal stem cells encoding cytosine deaminase suppress growth/metastasis of human breast cancer in mice. Branka Kavraki; R. Baddour; F. Muller; C. Wu; H. Wang; L. Zan; A. Chen.
transduced with the suicide gene hybrid yeast cytosine deaminase:uracil phosphoribosyltransferase (CD::UPRT). CD is a well-known enzyme that converts the prodrug 5-fluorocytosine (5-FC) into the therapeutic agent 5-fluorouracil (5-FU). The transduced ‘donor stem cells’ were characterized, expanded extensively, and then cryopreserved to create a master cell bank. ABs were produced by depriving CD::UPRT-expressing donor cells of nutrients in three-dimensional (3D) cultures, which naturally encouraged apoptotic cell death. The engineered ABs were enriched by differential centrifugation and filtration. Expression of CD::UPRT, as well as markers of apoptotic cells and EVs, was determined by RT-PCR and/or Western blots. Efficacy of the CD::UPRT-expressing ABs was evaluated in culture and then in vivo using a human breast cancer xenograft model. All animal procedures were approved by the IACUC of Texas A&M University and Baylor Scott&White Health. Results: The genetically modified ABs expressed high levels of CD::UPRT mRNA/protein, pro-apoptotic genes Bax and Bad, as well as common markers of EVs, including CD63 and CD81. Importantly, the ABs were readily internalized by breast cancer cells (BCCs) and transferred their therapeutic cargo. In the presence of 5-FU, CD::UPRT-expressing ABs showed remarkable ability to kill all cancer cell lines tested in vitro. Level of killing was dependent on time, concentration of 5-FU, and the number of ABs used in the assay. Moreover, the ABs suppressed BCC expression of genes involved in drug metabolism and metabolism, in immune-deficient mice harboring human breast tumors, intravenous injections of engineered ABs limited cancer growth and metastasis, an effect that was significantly augmented by systemic application of 5-FU. Importantly, the ABs did not cause substantial non-specific inflammation or damage. Conclusions: Taken together, the results here provide evidence that ABs have immense potential as carriers of therapeutic transgenes.

234

CPRIT Grantee
Poster Session A

Cisplatin triggers shifts in central carbon metabolism through changes in the tumor cell redox state Vlad Sandulescu, Baylor College of Medicine; W. Yu; Y. Chen; J. Dubrulle; F. Stossi; V. Putfuni; A. Sreekumar; N. Putfuni; D. Baluya; S. Lai

Introduction: Cisplatin is utilized in the treatment of multiple solid tumor histologies. Its anti-tumor effectiveness is primarily driven by DNA intercalation causing DNA damage. Prior to DNA intercalation, DNA binds to DNA binding proteins, which interact with cellular reducing equivalents. Our objective was to determine whether transient fluctuations in the cellular redox state are associated with measurable changes in central carbon metabolic flux. To answer this question we utilized a preclinical model of head and neck squamous carcinoma (HNSCC). Methods: We utilized a preclinical model of head and neck squamous carcinoma (HNSCC). Prevalently characterized, STR validated, HNSCC cell lines were used for measurements of cell death, cell cycle, senescence and metabolic changes. Platinum measurements were conducted using inductively coupled plasma mass spectrometry. Tumor metabolites were evaluated using a high-performance liquid chromatography / liquid chromatography mass spectrometry platform following administration of pan-labeled 13C glucose. Cisplatin effects on lactate production and tumor growth delay were measured using a previously described flank xenograft murine model of HNSCC. Results: Cisplatin binds DNA, generates DNA damage and decreases clonogenic survival in HNSCC. DNA-bound cisplatin represents a small fraction of total cellular cisplatin. Cisplatin interacts with the cellular redox state on a time scale consistent with that of DNA binding and DNA damage, triggering measurable drops in intra-cellular NADH/NAD+, and NADPH/NADP+. Ratios. Repression of cellular reducing potential using N-acetyl cysteine decreases cisplatin DNA binding, generation of DNA damage and cisplatin associated senescence and cell cycle arrest. Glucose consumption and metabolic flux of 13C labeled glucose flux generates pyruvate and lactate. Following cisplatin exposure, lactate levels are decreased, resulting in secondary shunting of labeled carbon into the citric acid cycle and pentose phosphate pathways. Conclusions: Cisplatin induced metabolic changes provide a unique opportunity for biomarker development and development of novel cisplatin sensitization strategies in HNSCC and other solid tumors.

235

CPRIT Grantee
Poster Session B

Alpha-ketoglutaric acid analogs functionally mimicking the oncometabolite D-2HG for epigenetic therapy of higher grade gliomas Kalkunte Srivenugopal, Texas Tech University Health Science Center at Amarillo; H. Madala; S. Punganuru

Introduction: Mutations at the active site of IDH1 gene (R132H) occur in >70% in lower grade malignant gliomas, and result in a dramatic accumulation of the oncometabolite D-2 hydroxylglutarate (D-2HG) in place of the normal metabolite alpha-ketoglutaric acid (AKG). AKG is a substrate for TET1, TET2 DNA-demethylases [5m-cytosine to 5-OH cytosine] and histone demethylases [H3-Lys27 to H3-K-met-1] that control the epigenetic landscape. D-2HG effectively competes with AKG and potently inhibits these enzymes leading to transcriptional silencing of targets such as the MGMT DNA repair, which removes the mutagenic alkylaion damage in gliomas. This may also explain superior therapeutic responses of IDH1-mutated gliomas to DNA alkylating agents. As a novel strategy, we hypothesized AKG derivatives that can replace AKG in epigenomic dioxygenase reactions will serve as potent anti-gloma drugs either by themselves or in combination with alkylating agents. Methods: We synthesized a D-2HG diethyl ester to enhance cellular uptake and tested in vitro effects on human brain tumor cell lines (DAOY, T98G, SF188 and UW18). Also synthesized a 2,4-dimethylglutaric acid (DMG), a AKG mimic with methylene groups inserted at the C2 and C4 positions. Effect of DMG in cell survival assays, oxidative stress assays, metabolic flux analyses, western blotting, and flow cytometry were used. Mitochondrial damage was assessed. Preclinical studies in normal mice and nude mice bearing intra cranial glioblastoma (luciferase expressing) xenografts were performed. Results: D2-HG ester at 5-10 mM and 24 h treatment caused moderate oxidative stress and inhibited MGMT, increased temozolomide cytotoxicity by 1.5 to 3-fold, and induced histone H3-methylations in glioma cells. The hydrophobic DMG-ester was more potent, by itself was cytotoxic with IC50 up to 500 µM, however, when combined at 100 µM with TMZ resulted in a great synergistic cell killing (9 fold, but 28-fold with UW-18 GBM cells). 0.25 mM DMG inhibited the cellular MGMT activity by 90%, inducing the expression of 8 genes that greatly increased the histone methylation (H1K25me1, me2 and H2B25me2). Other experiments showed a mild to strong, both acute and chronic induction of oxidative stress including elevated reactive oxygen species, decreased ATP, NADPH levels, and increased 5-hydroxy methyl cytosine and 5-hydroxy methyl cytosine levels, demonstrating oxidative damage. The orthotopic glioblastoma xenografts showed significant tumor regression. Conclusions: The AKG analogs can alter the cellular epithelial makeup and raise the tumor oxidative stress in a manner ascribed to D-2HG, and open up the much-needed exciting avenues of oncometabolite-based therapy for brain tumors.

236

CPRIT Grantee
Poster Session A

Structural modeling and hierarchical clustering of peptide-HLA complexes for cross-reactivity assessment Dinler Antunes, Rice University; K. Jackson; G. Vieira; G. Lisle; L. Kavkazi

Introduction: Immunotherapies that utilize cytotoxic T-cells have proven very effective at eradicating large tumor burdens in both animal models and human cancer patients. These therapies leverage special attributes of T-cells, such as the specific recognition of non-self peptides. Each T-cell expresses a unique T-cell receptor (TCR) that is capable of recognizing non-self peptides displayed by class I Human Leukocyte Antigen (HLA) molecules on the surface of tumor cells. This recognition can activate the T-cell and lead to the elimination of the tumor. Unfortunately, the progress of T-cell-based immunotherapies was tempered with reports of serious (even fatal) side effects. In fact, a given TCR can recognize different peptides displayed by different HLA molecules on the surface of tumor cells. This is referred to as T-cell cross-reactivity. As a consequence, there is a growing interest in elucidating the structural features driving T-cell activation and specificity. In addition, there is a need for the development of computational tools to help assess the risk for cross-reactivity in T-cell-based immunotherapies. Methods: Structural data of HLA complexes involved in described cases of cross-reactivity was obtained from the Protein Data Bank (PDB). Docking-based methods (e.g., DockTope and DINC) were used to model additional pHLA complexes of interest. Hierarchical clustering was used to predict structure-based similarities among modeled pHLA complexes and experimental pHLA complexes were confronted with available experimental data. Results: Our docking-based methods for pHLA structural modeling were capable of accurately reproducing known crystal structures, including key structural features for T-cell recognition. Moreover, our hierarchical clustering analysis was able to reproduce observed patterns of cross-reactivity among unrelated peptide-targets. Finally, the combined use of computational analysis and T-cell cytotoxicity assays provided structure-based explanations for observed inconsistencies in cross-reactivity experiments. Conclusions: Our results propose the protocol of combining structural similarity and T-cell cross-reactivity. Our analyses suggest that apparent inconsistencies in reported cross-reactivities, such as a preferential directionality, might also be driven by particular structural features of the pHLA complex. In addition, we provide evidence that structural analyses of pHLA complexes can be used as a predictive tool for cross-reactivity among unrelated pHLA-targets. Further work in this field will certainly contribute to safer T-cell-based immunotherapies.
Development of a novel non-diuretic brain-penetrating ethacrynic acid analog and demonstration of its potent efficacy in orthotopic glioblastoma

Kalkunte Srivenugopal, Texas Tech University Health Sciences Center at Amarillo; S. Punganuru; H. Madala

Introduction: The incidence of pediatric and adult brain tumors has continued to rise and there is an urgent need for new chemotherapy drugs. The BBB, intratumoral heterogeneity, overexpression of MGMT and bona fide anti-inflammatory drugs due to alkylating agents, are only a few problems preventing successful glioma therapy. We are interested in exploiting the elevated oxidative stress present in gliomas and have synthesized a hydrophobic, non-diuretic analog of ethacrynic acid (EA) called KSS72 [1,2-dichloro-4-methyl[1H]-1,2,3-triazole] by removing the -CH2- side chain. EA, by itself is not hydrophobic, is an inhibitor of GSTP1, and has weak anticancer effects. Methods: KSS72 was synthesized by standard chemistry and characterized. It retained alpha-beta carbonyl group of EA and underwent Michael addition. Pharmacokinetics of KSS72 after IP or oral administrations was performed in CD1 mice. Diuresis after administering a single-dose of EA or KSS72 to normal mice was compared. GSTP1 catalytic activity, ROS induction, cytoxicity against a panel of glioma cell lines, autophagy/apoptosis assays, and the efficacy of KSS72 in orthotopic glioblastoma xenografts were quantitated. Results: In contrast to EA (edecin used for hypertension), KSS72 was devoid of diuresis. It was 10-times more potent inhibitor of GSTP1 and exacerbated the redox imbalance in glioma cells. It was selectively cytotoxic to cancer cells including gliomas. Compared to EA which does not cross the BBB, pharmacokinetics following intravenous or oral administrations in mice showed its excellent penetration through the BBB, with KSS72 accumulating at levels equivalent to TMZ (25% of plasma levels) in the brain. In vitro assays measuring protein carbonyl content, GSH content, ROS generation, GST-pi enzyme activity and others showed that KSS72 triggers a redox imbalance by inhibiting GST-pi and by lowering the GSH and reducing equivalent (NADPH) levels, leading to a significant elevation of ROS. The upregulation of ER stress-responsive proteins, activation of MAPK, autophagy and apoptotic pathways by KSS72 were also noted in tumor cell lines. KSS72 also induced autophagy as a post event of redox perturbation. Nude mice bearing intracranial SF188 GBM mice (expressing luciferase) were given 25 mg/kg/day of KSS72 intraperitoneally for 2 weeks. There was a complete elimination of intracraniial tumors by bioluminescence and H&E staining of brain sections in all KSS72 administered animals. Conclusions: KSS72 acts through multiple pathways of oxidative stress and is a highly promising non-toxic anti-gloma drug with potential to enter clinical trials.

Identification of Potential K-Ras Inhibitors by Hierarchical Virtual Screening and Experiments

Amit Gupta, The University of Texas Health Science Center at Houston; S. Sarkar-Baranjee; P. Prakash; C. Pagba; X. Wang; J. Putkey; J. Hancock; A. Gorfe

Introduction: K-Ras is a small GTPase that plays a critical role in the regulation of cell growth and proliferation. Somatic mutations on K-Ras are associated with many different cancers, accounting for about 85% of all Ras-associated cancers and 25-30% of all human cancers. K-Ras is a very dynamic allosteric enzyme, and our previous studies revealed that K-Ras harbors four allosteric ligand-binding pockets and suggested that targeting these pockets is a feasible strategy to develop site-specific and selective inhibitors. These representative structures were used to target complementary pocket-specific chemical libraries from the large purchasable chemical space of the ZINC database. We performed ensemble docking of these tailored ligand libraries to each pocket with the standard precision (SP) module of the Glide docking software. The docking outputs were prioritized using hierarchical post-docking analysis based on common residue interaction patterns and chemical scaffold diversity. These hits were further tested using N15 heteronuclear single quantum coherence (HSQC) NMR, microscale thermophoresis (MST) and cellular assays. Results: Our K-Ras-harboring virtual screening yielded a list of about 100 compounds, and about 100 of these were tested for their ability to bind to K-Ras using HSQC NMR. Of the 100 tested, 10 compounds showed significant amide chemical shift perturbation at several residues, suggesting potential binding. The binding affinity of these compounds were calculated by MST, and their ability to interfere with RAS-RAF-MEK-ERK and RAS-PI3K-AKT signaling was monitored by measuring changes in the phosphorylation of ERK and AKT in BHK-21 cells expressing G12D K-Ras. Conclusions: Our combined hierarchical virtual screening and experiments yielded potential lead compounds targeting K-Ras. We will discuss these results and their implications for future efforts in K-Ras drug discovery.

Exploring flow effects on BOLD MRI with oxygen challenge in orthotopic lung tumor model Ralph Mason, The University of Texas Health Science Center at Houston; H. Zhang; J. Gross; J. Campbell; Z. Zhang; D. Saha; M. Takahashi; S. Zhang

Introduction: Blood oxygen level dependent (BOLD) can provide information on tumor oxygenation. However, the measurements are affected by blood flow, which is known to affect the signal of BOLD (so-called BLOOD: Flow and Oxygen Level Dependent). This is a particular concern for lung cancer imaging, where there are often large blood vessels around the region of interest. This study explored the extent of flow sensitivity by comparing the BOLD signal intensity and T2* values with and without flow suppression using an orthotopic lung tumor model. Methods: H460-luc human lung cancer cells were surgically implanted in the right hindlimb of 24 female nude rats. MRI (4.7 T) images were acquired in 15 rats using BOLD (multiecho gradient echo; TR = 150ms, ten echo time from 2 to 29 ms, flip angle = 20°) MRI was acquired with the intervention of an oxygen challenge (from air to 100% O2). Five sets of maps were acquired during air breathing and eight sets during oxygen breathing. Images were acquired in sagittal plane. BOLD was acquired with ECG triggering to avoid artifact effects. Spatial saturation bands were placed on each side of the imaging plane for flow suppression. We examined the effect of flow on temporal, spatial and regional basis. Results: T2* values increased in tumor and liver in response to oxygen. No temporal differences were noted between the tumor regions. T2* maps during air and oxygen breathing, as well as the ΔT2* (oxygen-air) showed negligible differences comparing the paired scans with and without flow suppression for tumor regions. However, the semi-quantitative %ΔSI maps showed different enhancement patterns. Statistical analysis was performed on the mean values from ROIs of tumor, liver and muscle of 16 rats. Most of the values were not significantly
different between the sequences. Greater differences were observed for the liver regions with two of the parameters (T2’-air and ΔT2’) reaching statistical significance. Strong correlations between the measurements were found in all four parameters. **Conclusions:** Quantitative measurements of BOLD appeared to be insensitive to flow for the tumor regions as observed in this preliminary study, while semi-quantitative ΔSI was strongly affected by flow. For well vascularized normal tissue (such as liver), flow suppression will be necessary for accurate measurements.

### 241 CPRIT Grantee Poster Session B

**Contemporary surgical outcomes of venous tumor thrombectomy managed with intraoperative Doppler ultrasound for kidney cancer**

**Sohn; K.**

**Cajipe; A.**

**Lee; T.**

**Hicks; E.**

**Sako; M.**

**Liss; W.**

**Chowdhury; R.**

**Rodriguez; D.**

**Kaukhi; S.**

**Introduction:** Radical nephrectomy (RN) with venous tumor thrombectomy (VTT) carries a significant morbidity and mortality risk. Examination of a contemporary single-institution series provides the capability to develop a management algorithm and examine its results. Our multidisciplinary integrated surgical pathway includes the use of intraoperative color Doppler ultrasound. We report our surgical outcomes after implementation of this technique. **Methods:** We retrospectively reviewed the records of all patients undergoing RN with VTT for kidney cancer from January 1, 2013 and October 1, 2016. VTT protocol includes intraoperative color Doppler ultrasound to precisely delineate the extent of VTT and guide cavotomy. Surgical complications, major postoperative complications (Clavien-Dindo classification ≥ 3), 30-day readmission rates, and outcomes data were reported. **Results:** Of 241 patients, 187 underwent RN with VTT. Twenty-six (45%) patients had Mayo Clinic level III or IV thrombus; of these, 19 required venovenous or cardiopulmonary bypass; three required patch grafting. There were fewer major bleeding complications with cautious administration of anticoagulation during the perioperative period. The median length of hospital stay was 8 days and there were 20 major complications. The 30-day readmission rate was 21% and the 90-day mortality rate was 8.9%. In multivariate analysis, low serum albumin and age-adjusted Charlson comorbidity score predicted length of stay; increased intraoperative blood loss was significantly associated with increased body mass index, serum creatinine, tumor thrombus level, and a history of significant weight loss >9.1 kg. Low serum hematocrit predicted 90-day mortality. **Conclusions:** Intraoperative color Doppler ultrasound is a useful tool and can facilitate caval preservation. Cavoversion can be avoided in most cases. Venovenous bypass can be avoided in many level III cases. Early therapeutic anticoagulation should be instituted with caution.

### 242 CPRIT Grantee Poster Session A

**Clinical and genomic landscape of gastric cancer with a mesenchymal phenotype**

**Jeong, Y.**

**Sohn, B.**

**Shin, J.**

**Lee, J.**

**Introduction:** Heterogeneity of gastric adenocarcinoma is reflected in the unpredictable outcomes when patients with similar stage of cancer are treated with empiric approaches. Molecular subtypes and their associated biomarkers need to be established to optimize therapy of gastric adenocarcinoma. **Methods:** We analyzed gene expression profiling data from 93 patients with gastric adenocarcinoma to uncover subtypes and identify a gene expression signature associated with prognosis and response to adjuvant chemotherapy. The association of the signature with prognosis was validated in four independent cohorts of 645 patients. **Results:** We identified 2 distinct molecular subtypes of gastric cancer: mesenchymal phenotype (MP) and epithelial phenotype (EP). Molecularly, MP subtype tumors showed high genomic integrity characterized by low mutation rates and microsatellite stability, whereas EP subtype tumors showed low genomic integrity. Clinically, the MP subtype tumors were associated with markedly poor survival and resistance to standard chemotherapy, whereas the EP subtype was associated with better survival rates and sensitivity to chemotherapy. **Conclusions:** Quantitative measurements of BOLD appeared to be insensitive to flow for the tumor regions as observed in this preliminary study, while semi-quantitative ΔSI was strongly affected by flow. For well vascularized normal tissue (such as liver), flow suppression will be necessary for accurate measurements.

### 243 CPRIT Grantee Poster Session B

**Development of an Effective Cancer Vaccine Platform Using Attenuated Salmonella to Deliver Recombinant Tumor-Associated Antigens**

**Xu, X.**

**Metelitsa, L.**

**Introduction:** Inadequate antigen delivery is one of the major limitations of modern cancer vaccine vectors. To overcome this challenge, we exploited Salmonella Pathogenicity Island 2 (SPI2) and its type III secretion system (T3SS) to deliver a tumor-associated antigen (TAA) of choice into the cytosol of antigen-presenting cells (APC) in situ. The goal of this study was to explore and exploit the potential of SPI2-encoded T3SS of clinically validated S. typhi strain CVD908 for construction of an effective cancer vaccine. **Methods:** We engineered the clinically validated S. typhi strain CVD908 to express SPI2-regulated dominant-negative oncoprotein survivin and MYCN. To adapt CVD908 to stably express recombinant antigens without antibiotic-dependent selection, we used a recently reported plasmid stabilization system that encodes a single-stranded binding protein (SSB), an essential protein in DNA metabolism, which was deleted from the bacterial chromosome. The SPI2-regulated expression cassette was then cloned into the SSB plasmid, so that the resultant construct maintained bacterial vector stability while expressing and translocating antigens in mouse model and human dendritic cells. **Results:** We found that CVD908-htrAssb vector effectively infects human dendritic cells in vitro and translocates recombinant human survivin and MYCN oncoproteins into their cytosol. DNA infection was sufficient to induce potent antigen-specific CTL responses able to recognize and kill tumor cells. Furthermore, CVD908-htrAssb remains stable and immunogenic in mice, not only increased the frequency of antigen-specific CTLs but also resulted in a dense tumor infiltration with CD8 T cells and enhanced antitumor activity in the neuroblastoma cancer model. **Conclusions:** Oral antigen delivery via SPI2-encoded T3SS of Salmonella typhi may be the foundation of an effective cancer vaccine platform and for clinical trials in human.

### 244 CPRIT Grantee Poster Session A

**Development of an Effective Cancer Vaccine Platform Using Attenuated Salmonella to Deliver Recombinant Tumor-Associated Antigens**

**Xin, X.**

**Baylor College of Medicine; L. Metelitsa**

**Introduction:** Inadequate antigen delivery is one of the major limitations of modern cancer vaccine vectors. To overcome this challenge, we exploited Salmonella Pathogenicity Island 2 (SPI2) to deliver a tumor-associated antigen (TAA) of choice into the cytosol of antigen-presenting cells (APC) in situ. The goal of this study was to explore and exploit the potential of SPI2-encoded T3SS of clinically validated S. typhi strain CVD908 for construction of an effective cancer vaccine. **Methods:** We engineered the clinically validated S. typhi strain CVD908 to express SPI2-regulated dominant-negative oncoprotein survivin and MYCN. To adapt CVD908 to stably express recombinant antigens without antibiotic-dependent selection, we used a recently reported plasmid stabilization system that encodes the single-stranded binding protein (SSB), an essential protein in DNA metabolism, which was deleted from the bacterial chromosome. The SPI2-regulated expression cassette was then cloned into the SSB plasmid, so that the resultant construct maintained bacterial vector stability while expressing and translocating antigens in mouse model and human dendritic cells. **Results:** We found that CVD908-htrAssb vector effectively infects human dendritic cells in vitro and translocates recombinant human survivin and MYCN oncoproteins into their cytosol. DNA infection was sufficient to induce potent antigen-specific CTL responses able to recognize and kill tumor cells. Furthermore, CVD908-htrAssb remains stable and immunogenic in mice, not only increased the frequency of antigen-specific CTLs but also resulted in a dense tumor infiltration with CD8 T cells and enhanced antitumor activity in the neuroblastoma cancer model. **Conclusions:** Oral antigen delivery via SPI2-encoded T3SS of Salmonella typhi may be the foundation of an effective cancer vaccine platform and for clinical trials in human.
ABSTRACTS

245 CPRIT Grantee Poster Session B

Targeted hypoxia reduction restores T cell infiltration and sensitivity to immuno therapy in prostate cancer Piyamaya Jayagavarak, The University of Texas M.D. Anderson Cancer Center; M. Al; P. Budhani; T. Bartkowiak; J. Sheng; C. Ager; C. Nicholas; A. Jaiswal; Y. Sun; K. Shah; S. Balasubramanayam; N. Li; G. Wang; J. Ning; A. Zal; T. Zal; M. Curran

Introduction: Tumors evade host immune responses through creation of an immune suppressive and hostile hypoxic microenvironment. T cell checkpoint blockade with anti-CTLA-4 and anti-PD-1 is effective in "hot" tumors like melanoma with pre-existing immune infiltrates. However, "cold" tumors like prostate and pancreatic cancers respond poorly. Hypoxia fosters metabolic alterations resulting in extracellular acidification of the microenvironment that can impair T cell function. Methods: We present here a platform to identify small molecule inhibitors of the mitochondrial UPRmt that can potentially be used as therapeutic strategy in selectively reducing cancer cell populations with low oxygen. Results: A collection of approximately 1300 small molecules yielded 298 UPRmt inhibitors, of which 43 repeated in the secondary screen. Conclusions: Current work is focused on validating these hits using similar compounds and/or genetic means (grant ID: RR160053).

246 CPRIT Grantee Poster Session A

A C. elegans platform for the identification of small molecule inhibitors of the mitochondrial UPR Mark Pellegrino, The University of Texas at Arlington; A. Qureshi

Introduction: The relationship between mitochondrial function and cancer has been considered for many decades. Otto Warburg was first to observe that cancer cells rely on mitochondrial respiration in the presence of oxygen that he believed was evidence of defective mitochondrial function and the source of its pathogenesis. This view has since changed and today, increasing evidence suggests that cancer cells actually rely on important mitochondrial activities such as the generation of energy through oxidative phosphorylation, and often times display enhanced organelle function. Nonetheless, it is clear that cancer cells are in need of mitochondrial recovery programs to survive including the stress response pathway known as the mitochondrial unfolded protein response (UPRmt). Here, mitochondrial stress activation of the bZIP transcription factor ATF4 (ATF4 mammals) results in the induction of a set of mitochondrial protective genes that help support repair of the organelle. Consistent with an activation of the UPRmt, multiple cancer cell lines display increased expression of known UPRmt target genes, including mitochondrial chaperones that help promote organelle homeostasis. Importantly, inhibition of the UPRmt pathways results in reduced survival of cancer cell populations but has negligible effects on healthy cells. This supports the targeting of the UPRmt as a possible therapeutic strategy in selectively reducing cancer cell populations without affecting neighboring healthy cells. Methods: With this in mind, we present here a platform to identify small molecule inhibitors of the UPRmt using the model organism C. elegans. We tested a collection of small molecules, including the Prestwick Chemical Library of FDA approved drugs, that could silence the UPRmt using a transgenic C. elegans UPRmt model as a read-out. Results: Our primary screen of approximately 1300 small molecules yielded 288 UPRmt inhibitors, of which 43 repeated in the secondary screen. Conclusions: Current

247 CPRIT Grantee Poster Session B

Preliminary Treatment Planning Guidance for Superior Radiation Treatments for Cancer Patients Christopher Kabat, The University of Texas Health Science Center at San Antonio; D. Defoor; N. Nikolopoulos; S. Stathakis; K. Shah; S. Balasubramanayam; N. Li; G. Wang; J. Ning; A. Zal; T. Zal; M. Curran

Introduction: Radiotherapy treatments are limited by the dose delivered to normal tissues. Conceptual and technological advances have led to new radiotherapy technologies (e.g. intensity modulated radiation therapy, rotational or helical delivery) which can deliver high dose to the tumor volume while sparing healthy tissues. During treatment planning the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations are employed to strategically guide us towards optimized treatment plans. Currently, RT plans are finalized and ready for delivery when QUANTEC criteria are met. Thus, current treatment plans often only meeting QUANTEC criteria and fail to further venture if doses to healthy tissues can be reduced. An application is purposed to address this issue by providing information to physicians and dosimetrist about the feasibility of reducing the dose to healthy tissue while maintaining tumor dose coverage. Methods: An application was developed using MATLAB software and incorporated theoretical dose distributions. For this study, a 10 MV VMAT delivery field was employed to generate optimized dose distributions for twenty previously treated patients. Each patient's TDD was calculated using their segmented tumor and organs at risk and their individual CT images. Tumor volumes were set to receive 100% of the evaluated dose, while the volume for the organs at risk were simulated based on our homegrown theoretical model using the information from a 10MV photon beam model. Results: For all twenty patient plans, our model demonstrates the possibility for improved tumor coverage and/or reduction of healthy tissue dose. Maximum dose to regions near tumor sites had minor differences, however distal regions contained greater sparing possibilities as predicted. Prostate cancer plans showed possible dose reduction for the rectum, without losing prostate coverage. Differences in the bladder dose between our TDD and delivered plans were more drastic, most likely due to varying bladder size of each patient and the proximity to the tumor. Conclusion: The TDD is a representation of the ideal treatment plan. The information that the TDD provides is used by the radiation dosimetrists and physicians as guidance during inverse optimization of the treatment plan. Our results have provided guidance in improving current treatment plans by indicating the volumes of healthy tissue where dose is distributed. Data collected from this study has provided insight into the challenges produced by altering dose distributions and developed an understanding of which dose distribution could possibly have the greatest improvements to patient plans.

248 CPRIT Grantee Poster Session A

Bone Targeted Nanoparticles for Metastatic Prostate Cancer Andrew Gdowski, University of North Texas Health Science Center at Fort Worth; A. Ranjan; M.arker; J. Vishwanatha

Introduction: Overall survival and serious toxicities in patients with bone metastatic prostate cancer remain problematic despite an expansion of therapeutic options approved in recent years. We have developed a bone targeted nanoparticle (NP) system to deliver cabazitaxel to bone lesions. The objective of this strategy is to increase therapeutic concentration at the bone metastasis site to achieve an improved therapeutic index. Methods: Poly (lactic-co-glycolic acid) NPs were fabricated with cabazitaxel encapsulation and subsequent conjugation of alendronate to the outer surface of the NP. Physico-chemical characterization of NPs was performed. In vitro studies with C4-2B and PC3 prostate cancer cell lines and spheroids were performed. Ex vivo NP bone affinity studies were completed. In vivo efficacy studies were conducted in male athymic nude mice implanted with intrasosseous tumors. After bone tumor development, mice were treated via tail vein injection with either saline, free cabazitaxel, non-targeted NPs, or targeted NPs for one month (starting n=6 per group. In addition, animal behavior experiments were performed on all treatment groups to assess functional status through gait analysis and pain through von frey filament assay. Results: NPs were successfully synthesized to size of 236 nm with a PDL of .120. High encapsulation efficiency and drug loading was achieved. Ex vivo bone binding experiment showed targeted NPs had 6 fold improved bone binding at 72 hours compared to non-targeted NP. Tumor efficacy experiment showed targeted NP and non-targeted NP had a statistically significant overall reduction in tumor measured by bioluminescence (P value <0.005). Interestingly, mice treated with targeted NP had no bone lesions on x-ray, whereas 100% of mice in saline group, 100% of mice in cabazitaxel group, and 33% of mice in non-targeted NP group developed...
bone lesions. Von frey assay showed a significant reduction in relative response in the targeted NP group (P value < 0.005). Conclusions: We have successfully synthesized a bone targeted NP system. In this project, we have shown that targeted NPs help maintain bone structure in tumor burdened limbs as well as decrease tumor size. Emerging evidence suggests that epigenetic alterations contribute to the development of endocrine resistance. Enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, is frequently overexpressed in breast cancer and strongly associated with aggressive phenotypes of cancer cells. However, the involvement of EZH2 in endocrine resistance remains poorly understood. Here we discovered a critical transcriptional axis consisting of EZH2, ERα, and its corepressor GREB1 in driving estrogen resistance (Tamr). Methods: Association between EZH2 and tamoxifen resistance was investigated bioinformatically, qRT-PCR, Western blot, cell proliferation assays and immunohistochemistry (IHC) staining. RNA-seq and proteomics were applied on cell lines to reprogram the specific transcriptionists to favor the endocrine resistant phenotypes. Xenograft models were established to further validate the efficacy of EZH2 inhibitors in vivo. Results: Our studies demonstrated that higher EZH2 levels are associated with poorer response to tamoxifen in breast cancer patients. EZH2 represses the expression of the ERα co-factor GREB1 by maintaining DNA hypermethylation of a particular CpG-enriched region at the GREB1 promoter, which is negatively correlated with GREB1 levels in clinical specimens and highly associated with cell sensitivity to endocrine treatment. We also revealed a novel function of GREB1 in endometrial cells: it regulates the expression of different genes recruited by the distinct sets of ERα cofactors to cis-regulatory elements. This explains the opposing biological effects of GREB1 on breast cancer cell growth in response to estrogen or anti-estrogen. EZH2-dependent repression of GREB1 in hormone refractory cells results in chromatin relocalization of ERα, reorganizing the anti-estrogen into an agonist. Levels of EZH2 and GREB1 are negatively correlated in clinical samples from patients receiving adjuvant tamoxifen treatment, and together predict response to endocrine therapy. Conclusions: Our work provides insights into an epigenetic mechanism of endocrine therapy resistance and a potential novel therapeutic strategy to overcome tamoxifen resistance in aggressive breast cancer.

251 CPRIT Grantee Poster Session B

Proteolytic hinge cleavage of the HER2-targeting antibody pertuzumab impairs its ADCC function and antitumor activity Xuejun Fan, The University of Texas Health Science Center at Houston; H. Hsiao; R. Jordan; N. Zhang; Z. An

Introduction: Proteolytic impairment of monoclonal antibodies (mAbs) in the tumor microenvironment compromises the efficacy of therapeutic antibodies such as the HER2 targeting antibody trastuzumab and serves as one of the cancer immune evasion mechanisms. Specifically, proteolytic cleavage at a susceptible peptide bond in one of the two strands of the hinge region of human immunoglobulin G1 (IgG1), termed single hinge cleavage, renders an IgG1 antibody dysfunctional as regard to its Fc effector functions such as ADCC, ADCP, and CDC. Pertuzumab is a humanized IgG1 monoclonal antibody targeting the epidermal growth factor receptor (HER2/ErbB2) and has been widely used in the clinic in combination with trastuzumab for treatment of HER2 overexpressing breast cancer and other cancer types. The effect of single proteolytic hinge cleavage of pertuzumab on its Fc effector function and anti-tumor efficacy has not been studied. Methods: In this study, we determined the single hinge cleavage of pertuzumab (IgG-P) in high HER2 expressing cell cultures. Single hinge cleaved pertuzumab (sclgG-P) was evaluated for its ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) activity using a xCELLigence instrument, and anti-tumor efficacy was assessed in a mouse xenograft tumor model as compared to intact pertuzumab. In addition, we constructed a protease-resistant version of anti-hinge cleavage site monoclonal antibody (AH-mAb) and assessed its efficacy in trastuzumab treated tumor-bearing mice. Results: Our single hinge cleavage pertuzumab impairs its ADCC function and antitumor activity due to proteolytic impairment. Further, we tested the effect of a combination treatment applying pertuzumab and trastuzumab on the single hinge cleavage and ADCC activity in vitro. Results: Single hinge-cleavage of pertuzumab caused substantial loss of ADCC activity and reduced tumor efficacy in tumor cell lines expressing high levels of ADCC function that has never before been shown in a PDAC case. Looking forward, our model not only may be used to discover new drug candidates and elucidate novel mechanisms, but may also be the first step towards the establishment of a true precision medicine paradigm for PDAC.

252 CPRIT Grantee Poster Session A

Relative Biological Effect of Proton Therapy in Hypothyroidism Pablo Yepes, Rice University; D. Mirkovic; R. Mohan; U. Titt; A. Adair

Introduction: Compared with traditional photon therapy, protons have unique and highly attractive physical properties in that they have a finite range in tissue, high dose at the end of their range, and relative biological effectiveness (RBE) of protons compared to photons, is a constant of 1.1. Many in-vitro and in-vivo studies indicate that RBE is a complex function of dose, linear energy transfer (LET), tissue type, and the endpoint. However, there is very little clinical evidence for variable RBE. In order to bring PT to its full potential a better understanding of its RBE needs to be achieved using clinical data. Methods: We have...
performed a retrospective study of patients treated with proton therapy, whose thyroid received a significant radiation dose (>20 Gy), and were followed for symptoms of hypothyroidism. Conclusion: The Complication Probability (NTCP) was calculated as a function of volume and mean dose. The mean Dose was calculated with a Monte Carlo program using a fixed RBE=1.1 and with two models of variable RBE. The obtained NTCP for the three cases were compared with the NTCP obtained for a single patient treated with photons. Results: The NTCP results obtained for protons with the variable RBE models were closer to the NTCP curve for photons. This suggests that the assumption of a fixed RBE for protons may lead to an underestimate of the dose actually delivered. Conclusions: To our knowledge this is one of the first studies where clinical results are utilized to improve our knowledge of the true RBE for proton therapy. It demonstrates that retrospective analysis of clinical outcomes combined with accurate dose calculation could lead to a significant improvement in our understanding of biological characteristics and, eventually, outcomes of proton therapy.

253

CPRIT Grantee Poster Session B

Direct measurement of a change in biological damage between low and high energy x-ray beams using a novel DNA dosimeter Kristen McConnell, The University of Texas Health Science Center at San Antonio; X. L. M. Obeidat; N. Kirby; E. Shim

Introduction: Published data indicates that low energy x-rays, as compared with higher energy x-rays, have higher relative biological effectiveness (RBE). Conventional detectors for radiotherapy dosimetry are incapable of directly measuring this increase in biological damage. Methods: A DNA dosimeter consisting of magnetic streptavidin beads attached to 4 kilobase pair DNA strands labeled with biotin and fluorescein amidite on opposing ends was created. mNS-5 cells were passaged and cultured in RHB-A media. Both were irradiated over a range of doses in low (160 kVp) and high (6 MV) energy x-ray beams. A RaySafe Xi R/F detector was used to verify the dose in the low energy (Faxtron Model 43955F) and the beam energy (Varian 600 C/D). Probability of DSB (PDSB) was measured by DNA dosimeters, and survival fraction was computed for the mNS-5 cells. Doses corresponding to the same level of damage (PDSB or SF) between the low and high energy beams were identified and used to calculate RBE. Results: For the DNA dosimeter, 6 Gy in the low energy beam produced the same PDSB as 7.62 Gy in the high energy beam, yielding an RBE of 1.27±0.12. Additionally, a mouse neural stem cell (mNS-5) was used as a biological RBE reference. A DNA dosimeter consisting of magnetic streptavidin beads attached to 4 kilobase pair DNA strands labeled with biotin and fluorescein amidite on opposing ends was created. mNS-5 cells were passaged and cultured in RHB-A media. Both were irradiated over a range of doses in low (160 kVp) and high (6 MV) energy x-ray beams. A RaySafe Xi R/F detector was used to verify the dose in the low energy (Faxtron Model 43955F) and the beam energy (Varian 600 C/D). Probability of DSB (PDSB) was measured by DNA dosimeters, and survival fraction was computed for the mNS-5 cells. Doses corresponding to the same level of damage (PDSB or SF) between the low and high energy beams were identified and used to calculate RBE. Results: For the DNA dosimeter, 6 Gy in the low energy beam produced the same PDSB as 7.62 Gy in the high energy beam, yielding an RBE of 1.27±0.12. Conclusions: Given the RBE agreement, the DNA dosimeter can be used to directly measure the biological effect of radiation. More refinement and measurements will be performed to confirm these results.

254

CPRIT Grantee Poster Session A

Novel scoring algorithm for patient specific radiotherapy plan evaluation Ara Alexandrian, The University of Texas Health Science Center at San Antonio; S. Stathakis

Introduction: A unique feature of radiation oncology is the ability to visualize how radiation interacts in a patient’s anatomy before any dose is administered by integrating intracavitary beam modeling with CT scans. This feature enables the creation of sophisticated treatment plans, but never answers the question of whether the current treatment plan can be improved to the best possible plan. By providing physicians a metric to evaluate treatment plan performance, it would allow them to empirically ensure radiation oncology patients receive optimal care. A novel scoring algorithm has been developed to quantify how effective a treatment plan is in delivering dose to the tumor. The algorithm geometrically evaluates the area between the dose volume histograms of critical structures to ensure that the delivered dose is as close to the NTCP curve for photons as possible. Methods: Treatment plans are evaluated by analyzing the dose volume histograms of critical structures to see if they meet literature established criteria points. Our scoring algorithm geometrically evaluates the area between the dose volume histograms of structures independent from matched voxel points to determine the score. We have applied our scoring algorithm to a variety of treatment plans and have found that our scoring algorithm produces a better score than a plan with less area between a curve and its criteria points results in a better score than a plan with less area between a curve and its criteria points. The scoring algorithm uses a polygon-based area integration to assess how well the dose volume histograms match with content-based criteria points. After computing an area for all criteria points in all structures, the areas are summed to give a composite score for the treatment plan. Results: With our scoring algorithm, we are capable of scoring radiotherapy treatment plans such that a quantized metric provides a more complex indicator of plan quality than previously existed. Conclusions: Development of a robust scoring algorithm for treatment plans reduces the uncertainty about whether cancer patients are receiving optimal treatments prior to radiation delivery. In addition to improving treatment plans, in the short term, a robust algorithm can improve the standard of care in the long term by training a machine learning algorithm to avoid features from poorly scored past plans in the automation of future plans.

255

CPRIT Grantee Poster Session B

Digital histopathology and automated learning to interpret chemotherapy response in high-grade osteosarcoma Patrick Leavey, The University of Texas Southwestern Medical Center; H. Arunachalam; R. Mishra; D. Leonard; A. Sengupta; D. Rakheja; O. Guiberteau

Introduction: Response to pre-operative chemotherapy, estimated by histological evidence of necrosis, has been the most important prognostic indicator for patients with non-metastatic osteosarcoma for 3 decades. However, efforts to adjust therapy based on this have to date been unsuccessful. We propose to refine the interpretation of chemotherapy response, utilizing advances in digital imaging and automated learning. Methods: Fifty patients diagnosed with high-grade osteosarcoma at Children’s Medical Center Dallas between 1995-2015 were identified. Resected specimens after chemotherapy were processed with standard procedures to provide the largest surface area for histology evaluation of tumor response. Using a pre-determined grid, each of the 20× stained sections was harvested to produce a single histology glass slide, which was then digitized as whole slide image (WSI). Each WSI allows for viewing across multiple resolutions of up to 40× magnification, while each magnified field is represented by a digital tile. Nine-hundred and forty-two histology slides (mean 19 slides/patient; 45-51 slides) were digitized from a set of 40 WSIs, representing features of viable tumor (VT), necrotic tumor (NEC) and areas of non-tumor (NT). 1,144 feature tiles at 10x magnification were randomly identified for annotation, segmentation and development of automated learning algorithms. Annotation was performed by two pathologists, classifying tiles and areas within tiles into VT, NEC and NT areas, using a purpose-built tool. As an initial validation step, both machine learning and deep learning neural networks were trained with these 1,144 tiles. Results: Unsupervised deep learning neural network models achieved 92% accuracy, network with 90% accuracy and NT with an accuracy of 95%. Supervised classical machine learning methods using support vector machines resulted in an average accuracy of 89.9% with per class accuracy of 91% for VT, 87% for NEC and 91% for NT. Conclusions: We have completed the 1st step in validating an automated learning tool to refine the interpretation of chemotherapy response in osteosarcoma. In the next phase, we will continue to optimize automated learning and interrogate tumor features from all 942 WSIs. We will compare this output to the chemotherapy response estimate by two pathologists blinded to each other’s estimation of necrosis and to the clinical value generated at the time of surgery.

256

CPRIT Grantee Poster Session A

Targeting Barrett’s stem cells to preempt esophageal adenocarcinoma Marcin Duleba, University of Houston; J. Xie; Y. Liu; R. Mahalingam; D. A. Mongin; G. Xie; C. Stepham; K. Ho; J. Ajani; P. Davies; W. Xian; F. McKeon; W. Kern

Introduction: Three million Americans have a condition known as Barrett’s esophagus (“Barrett’s”), a precancerous metabolastic lesion that can progress, through low- and high-grade dysplasia, to highly lethal esophageal adenocarcinoma. Current standard-of-care for Barrett’s patients includes arduous and expensive endoscopic monitoring for the detection of dysplasia, as well as non-specific physical ablation of these regions. We have employed advanced stem cell techniques to propagate is individual cell lines (Wang et al., 2015; Yamamoto et al., 2013). Patient-matched stem cells of Barrett’s and adjacent esophageal epithelia, and have now adapted these stem cells to 384-well formats for high-throughput screening of small molecule libraries in an effort to identify ones that selectively eliminate Barrett’s stem cells and adjacent esophageal epithelia, and have now adapted these stem cells to 384-well formats for high-throughput screening of small molecule libraries in an effort to identify ones that selectively eliminate Barrett’s lesions for preemptive therapeutic strategies. Methods: Patient-matched stem cells from normal Barrett’s were cloned at the single cell level from 1mm endoscopic biopsies and propagated in individual cell lines (Wang et al., 2015; Yamamoto et al., 2016). After characterization by whole genome expression analysis, 3-D differentiation, and epigenetics profiling, these stem cell lines were grown as colonies in 384-well formats for identifying known and drug-like small molecules that selectively eliminate Barrett’s stem cells. Results: The screening platform comparing patient-matched stem cells of Barrett’s and esophageal epithelia is robust and yields highly reproducible results (Z-factor 0.89). We have identified a number of known and experimental drugs that eliminate Barrett’s stem cells at concentrations far below those...
affecting normal esophageal stem cells, and many of these cluster into several discrete bins of chemical and functional similarity. In our co-culture model of Barrett’s and normal esophageal stem cells, we successfully eliminate Barrett’s while enabling repair by the unaffected esophageal stem cells. These data have now been extended to five additional Barrett’s cases that behave in a similar manner in response to these drugs and drug candidates. Conclusions: We have successfully adapted ground state stem cells showing potential for high-throughput drug screening and have identified multiple lead compounds that selectively eliminate Barrett’s stem cells in this format and in culture models of Barrett’s and esophageal epithelia. We are presently analyzing compounds from different functional classes for synthetic lethal effects to optimize a potential therapeutic regimen that could specifically eliminate Barrett’s and dysplastic Barrett’s to enable repair by adjacent normal epithelia.

257

CPRIT Grantee Poster Session B

Novel strategies for preventing colorectal cancer in inflammatory bowel disease

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Introduction: The 1.5 million Americans with inflammatory bowel disease (IBD), approximately 200,000 will die of an unusual form of colorectal cancer (CRC) that is both multifocal and enormously difficult to detect. As IBD is the key risk factor for this type of CRC, efforts to mitigate IBD itself, though metadata with IBD therapies such as purine analogs and anti-TNF alpha inhibitors do not support a preventive property of these drugs. Using advanced stem cell cloning technologies, we have discovered that patients with IBD possess two types of colonic stem cells including normal ones seen in patients without IBD and one marked by potentially pathogenic features. This novel, IBD-associated colonic stem cell expresses a hyperinflammatory gene signature, shows defective barrier function upon differentiation, and is 100-fold more sensitive to the toxins of C. difficile, a bacterium linked to nosocomial cases of diarrhea. We have adapted IBD patient-matched normal and pathogenic stem cells to 384-well screening format to identify drugs that might selectively eliminate the pathogenic stem cells and the risk they present for CRC in patients with IBD. Methods: Stem cell clone libraries are generated from endoscopic biopsies of terminal ileum, colon, and rectum of patients with Crohn’s and ulcerative colitis as well as control patients without IBD. Stem cells are grown on irradiated 3T3 cells in media that maintains their normal phenotype status we previously described (Wang et al., 2015; Yamamoto et al., 2016). Results: The patient-matched normal and IBD-linked stem cells yield highly reproducible data from differential drug screens of various bioactive, experimental, and drug-like small molecule libraries. We are presently leveraging combinations of C. difficile toxins and low concentration, at very low cost, antitumor small molecules with optimal synthetically lethal therapies directed at the aberrant stem cell that likely drives both the IBD and the CRC that arises in patients with these conditions. Initial screens of these candidates on these patient-matched stem cells sensitized with very low concentrations of C. difficile toxins show synthetic lethality toward the IBD-linked stem cell with low concentrations of candidate small molecules. Conclusions: High rates of CRC in IBD patients remain an unsolved medical need. We have discovered epigenetically altered mucosal stem cells in IBD patients that likely underlie this disease, as well as small molecule and biological drugs that eliminate them selectively while sparing stem cells with normal phenotypes from the same patient.

258

CPRIT Grantee Poster Session A

FDA-approved Drugs Inhibit Oncogenic RUNX1-ETO in Acute Myeloid Leukemia with Chromosome Translocation t(8;21)

Yongcheng Song, Baylor College of Medicine; L. Lu; Y. Wen; Y. Yao; F. Chen; G. Wang; F. Wu; J. Wu; P. Narayanan; M. Redell; Q. Mo

Introduction: Acute myeloid leukemia (AML) is a major blood cancer with poor prognosis. New therapies are needed to target oncogene driven leukemia stem cells, well known account for relapse and resistance. Chromosome translocation t(8;21), which produces RUNX1-ETO (R-E) fusion oncogene, is found in ~13% AML. R-E dominant-negatively inhibits global gene expression regulated by RUNX1, a master transcription factor for hematopoiesis, causing increased self-renewal and TNP cell state differentiation of hematopoietic progenitor cells, and eventually leukemia initiation. Methods: Bioinformatics methods followed by biological activity testing were used to find compounds that can inhibit R-E mediated gene expression. Molecular biology studies were conducted to find a possible molecular mechanism. Results: Connectivity-Map was used to find candidate compounds that can alter gene expression pattern as R-E knockdown does in t(8;21) AML. It yielded 78 compounds showing selective activity against Kasumi-1 cells. The most active compounds are several FDA-approved drugs showing low mIC50 activity against Kasumi-1 leukemia including, primary care medications, as low as >1000-fold selectivity. These compounds are non-cytotoxic. Rather, they inhibited the R-E mediated gene expression and reactivated that of RUNX1, which caused significant differentiation and apoptosis. Particularly noted are potent activities (as low as 2 nM) against self-renewal and R-E dominant-negative function in a co-culture model of R-E containing leukemia cells. This is therefore a targeted therapy. Conclusions: Favorable human PK, highly potent and selective activities of these drugs as well as synergism in combination therapies strongly support that these drugs could be used in the clinic to treat AML with t(8;21) chromosome translocation.

259

CPRIT Grantee Poster Session B

Dihydroceramide increase precedes golgi dispersal, pro-survival autophagy, ER stress, and UPR in fenretinide + safingol treated neuroblastoma cells

Nikhil Vad, Texas Tech University Health Sciences Center; D. Wang; H. Cho; D. Verlekac; K. Linch; C. Reynolds; M. Kang; B. Maurer

Introduction: We have reported that fenretinide (4-HPR) is active against high-risk neuroblastoma (NB) in vitro and in vivo; our Phase I trials of novel 4-HPR formulations evidenced clinical activity. Mechanisms of activity include increase of cytotoxic dihydroceramides. Fenretinide activity in vitro is enhanced by safingol (S), the L-threo diastereomer of sphinganine. Here, we identify stress pathways activated in response to 4-HPR+S and identify iaxazomib, a pro tease inhibitor, and antimalarial, mefloquine, a disruptor of autophagy, as new potential synergizing agents for 4-HPR+S. Methods: Sphingolipids were assessed by LC/MS/MS; cytotoxicity by fluorescence-based plate assay in 2% and 5% oxygen; apoptosis by TUNEL assay. Organelles, ER stress markers, unfolded protein response (UPR), and autophagy, were assessed using immunoblotting, immunoprecipitation, and electron/confocal microscopy. Target validation was carried out by silencing r-e sensitizing drugs. Results: 4-HPR rapidly increased D-erythro-dihydroceramides; safingol was cataleolized to L-threo-dihydroceramides. Safingol (2-3 μM) caused multi-log cytotoxic synergy of 4-HPR in eight of ten GBM and five NB cell lines (Cl<0.7). Treatments resulted in golgi fragmentation (+6-12h) without decrease of stack proteins, GM-130, α-Mannosidase-II, and TGN-38, and preceded increase of ER stress transducer, GRP78, critical for manifestation of unfolded protein response (UPR) and pro-apoptic CHOP protein; UPR was evidenced by increase of poly-ubiquitinated proteins and increased autophagic flux (+12-48h). Cell death was apoptotic (cleaved caspase-3/PARP, TUNEL-positive) and not necrotic (cleaved caspase-9/12/7). ER stress was assessed by mefloquine, or siRNA-silencing of BECN1 or ATG7, temporally-accelerated cytotoxicity and increased total apoptosis (p<0.05) in GBM cells. Consistent with cytotoxicity being dependent on misfolded protein stress, iaxazomib further increased ER stress markers and accelerated/ increased autophagy (p<0.05). This corresponded with decrease of tyrosine phosphorylation of p97/VCP, an AAA+-ATPase critical for the fusion of transitional ER membrane vesicles into golgi stacks. Knockdown of p97/VCP recapitulated features of 4-HPR+S treatment, including golgi fragmentation and increase of ubiquitinated proteins and autophagic vacuoles. Treatment with D-erythro-sphinganine plus dihydroceramide desaturase inhibitor, GT-11, plus safingol increased both D-erythro- and L-threo-dihydroceramides and recapitulated morphological, biochemical, and cytotoxic effects. Conclusions: Delineation of response pathways allowed the identification of mefloquine and iaxazomib as new potential combinatorial agents to enhance 4-HPR+S. Combinatorial NB xenografts are in progress. Intravenous fenretinide is in progress. Phase 2 trial in PTCL. An adult Phase I trial of fenretinei + safingol is in progress in the South Plains Oncology Consortium.

260

CPRIT Grantee Poster Session A

Cancer vaccine formulation dictates synergy with CTLA-4 and PD-L1 checkpoint blockade therapy

Yared Hailiemichael, The University of Texas M.D. Anderson Cancer Center; W. Overwijk

Introduction: Therapeutic blockade of the checkpoint receptors, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), on T cells can cure patients with metastatic cancer. However, many patients do not experience clinical benefit and significant hurdles remain in increasing checkpoint blockade therapeutic benefit. Anti-cancer vaccination is a promising approach to increase the efficacy of checkpoint blockade therapies. However, the landmark FDA registration trial for anti-CTLA-4 therapy revealed a complete lack of benefit of
adding vaccination with gp100 peptide formulated in incomplete Freund's Adjuvant (IFA). Thus, it is currently unclear how to combine anti-CTLA-4 or by extension anti-PD-1/anti-PD-L1 with vaccination. We recently reported that vaccination with gp100 peptide in IFA creates a persisting antigen depot that primes antigen-specific CD8+ T cells, followed by their undesirable sequestration at the vaccination site, and eventually their exhaustion and apoptosis, resulting in negligible anti-tumor activity. Alternatively, we understand that the mechanism which vaccination fails to synergize with checkpoint blockade therapy, we studied the widely used standard treatment model of anti-CTLA-4 therapy of established subcutaneous B16 melanoma and added concurrent vaccination with gp100/IFA together with adoptively transferred transgenic TcR pmel-1 T cells that specifically recognize the gp100 melanoma. For a more comprehensive assessment of anti-CTLA-4 and vaccine activated CD8+ T cells (Teffs), we included CD44, CD11a and CD8 to better quantify their number and survey their localization at the tumor and vaccination site. Results: Here, we show that gp100 vaccination induces gp100-specific Teff which dominantly force trafficking of anti-CTLA-4-induced, non-gp100-specific Teff cells away from the tumor, reducing tumor control. The inflamed vaccination site subsequently also sequesters and destroys the systemic pool of anti-CTLA-4 induced Teff with specificities for tumor antigens other than gp100, reducing the anti-tumor efficacy of anti-CTLA-4 therapy. Mechanistically, Teff at the vaccination site recruited inflammatory monocytes, which in turn attracted additional Teff in a vicious cycle mediated by IFN-g, CXCR3, ICAM-1 and CCL2. This process was dictated by the specific vaccine formulation, and altering the vaccine formulation prevented the inflammatory cascade and resulted in potent antitumor effects with the anti-CTLA-4 checkpoint blockade. Conclusions: In conclusion, gp100/IFA vaccination induces an inflamed vaccination site that recruits, functionally impairs and eventually destroys tumor-specific Teff induced by anti-CTLA-4 checkpoint blockade therapy thus severely limiting the antitumor effect. The unfavorable side-effect of the persistent vaccine formulation and synergizes with anti-CTLA-4 and/or anti-PD-L1 therapies, resulting in significantly improved anti-tumor activity.

261

CPRIT Grantee Poster Session B

GSK3-beta regulates epithelial-mesenchymal-transition and cancer stem cell properties in triple-negative breast cancer Rama Soundararajan, The University of Texas M.D. Anderson Cancer Center; G. Vijay; M. Toneff; J. Chang; J. Rosen; S. Mani

Introduction: Triple-negative breast cancers (TNBCs), which lack receptors for estrogen, progesterone, and amplification of epithelial growth factor receptor 2, are highly aggressive. Consequently, patients diagnosed with TNBCs have reduced overall- and disease-free survival rates compared to patients with other subtypes of breast cancer. TNBCs are characterized by the presence of cancer cells with mesenchymal properties, which may be due to epithelial-mesenchymal-transition (EMT) and plays a major role in the progression of this disease. The EMT program has also been implicated in chemoresistance, tumor recurrence, and induction of cancer stem cells (CSC) properties. Currently, there are no targeted therapies available for TNBC. This study was hence focused on identifying novel EMT targets to treat TNBC. Methods: We performed a published patient gene expression databases to identify EMT-associated genes predictive of poor clinical outcome in TNBC. We also simultaneously conducted a high throughput drug screen to select compounds that could serve as modifiers of novel therapeutic targets for TNBC, and shortlisted GSK3-beta inhibitors for further studies. Using drug sensitivity assays, we tested both epithelial and mesenchymal breast cancer cells for preferential loss of viability towards GSK3-beta inhibitors. We next profiled these cell populations for surface cancer markers (CD44+CD24-, FACS) and functional mammosphere-forming ability, to test if GSK3-beta inhibition affects mammosphere formation. We also tested the ability of selected GSK3-beta inhibitors to alter the EMT-related migratory properties of mesenchymal breast cancer cells (using wound-healing assays), as well as the expression of mesenchymal markers (by immunoblotting). Results: We observed that enhanced expression of GSK3-beta leads to a loss of cancer stem-like properties within the PTPN11 (SHP2-encoding gene) exon signal pathway, correlated with poor overall patient survival. We concurrently identified the GSK3-beta inhibitor in our drug screen as one of the most potent inhibitors of EMT, supporting our clinical observation. We found that GSK3-beta inhibitors selectively kill cancer cells with mesenchymal attributes, while sparing cells with epithelial properties. Furthermore, GSK3-beta inhibitors decreased both the CSC properties of mesenchymal cancers, as well as the expression of mesenchymal markers. Inhibition of GSK3-beta also reduced EMT-related migratory properties of mesenchymal breast cancer cells. Conclusion: In conclusion, our data demonstrates that GSK3-beta is a novel therapeutic target for CSC-enriched TNBCs, and that GSK3-beta inhibitors may serve as selective inhibitors of EMT and CSC properties for the treatment of aggressive TNBC.

262

CPRIT Grantee Poster Session A

Spinal Nerve Tolerance to Single-Session Stereotactic Ablative Radiotherapy Paul Medin, The University of Texas Southwestern Medical Center; B. Hrycushko; L. Phillips; J. Sayre; R. Foster; A. Van der Kogel

Introduction: Stereotactic ablative radiotherapy (SABR) is a rapidly expanding treatment modality utilized for an increasing number of cancers. The radiosensitivity of healthy normal tissues, including neural structures, is poorly understood. In the setting of SABR, numerous cases of peripheral neuropathy following SABR have been published. A better understanding of tolerated dose limits is critical to avoid overestimation, thus prescribing radiation doses that will lead to catastrophic normal tissue injury or underestimation in resulting in lower prescriptions, which are less likely to ablate tumors. A study to define the dose-related incidence of neuropathy resulting from single-session SABR to the spinal nerve using a porcine model. Methods: To date, 25 Yucatan minipers have been entered into this study. Each animal has received CT and MRI scans for treatment planning followed by single-session SABR using an image-guided, 6MV linear accelerator. A 1.5 cm length of the left-sided C6, C7 and C8 spinal nerves was targeted. Animals were distributed into 5 dose groups receiving 16(n=7), 18(n=5), 20(n=5), 22(n=5) or 24(n=3)Gy. The neurologic status of all animals is being followed by electrodiagnostic exam (-1, 2, 10, 20, 30, and 50 weeks) and daily observation of gait. Currently, all animals have been followed until gait change or a minimum 46 weeks after irradiation. Animals will continue to be evaluated with electrodiagnostic exams and gait observation until gait change occurs or the 52-week maximum followup period is reached. Histopathologic examination has been performed on the irradiated spinal nerves and the corresponding unirradiated contralateral nerves of 16 pigs. Results: To date, a change in gait has been observed in animals that were in the 18(n=25)/20(n=5)/22(n=5)/24(n=3)Gy dose groups presenting a clear dose-response curve. The animals presented with a limp in their hindlimbs and electromyography demonstrated evidence of denervation in C6 and C7 innervated muscles. Deficits were first observed 9-15 weeks following irradiation. All symptomatic pigs had demyelination and fibrosis in their irradiated nerves while contralateral nerves showed normal morphology. Conclusions: The neurologic deficits observed following spinal nerve irradiation have occurred at the same dose levels and latency periods as observed in our previous study of spinal cord tolerance; however, spinal nerves were irradiated along with the spinal cord in our previous study. We conclude that the tolerance of the spinal nerve must be less than or equal to the tolerance of the spinal cord.

263

CPRIT Grantee Poster Session B

SHP2: sailing against tumor-mediated inhibition of chimeric antigen receptor T-cell therapy Khaled Sanbar, Baylor College of Medicine; C. C. Lee; L. Brunetti; M. Mukherjee; N. A. Ahlawat, M. Hegde

Introduction: A phase I study of autologous HER2-specific chimeric antigen receptor (CAR) T-cells for progressive glioblastoma (GBM) demonstrated an excellent safety profile and tumor regression/stabilization in 8/16 evaluable patients resulting in improved median survival. However, GBM is highly immunosuppressive and can dampen the function of CAR T-cells by exploiting multiple co-inhibitory pathways. While concurrent immune-checkpoint blockade using monoclonal antibodies may improve the anti-GBM activity of CAR T-cells, the unreliable pharmacokinetics of antibodies in the CNS remains a challenge. Therefore, our lab attempted to convert the native PD-1/PD-L1 inhibitory signal into a stimulatory one by expressing PD-1 fusion molecules (native PD1extracellular domain linked to a stimulatory intracellular domain: 41BB or CD28) in HER2 CAR T-cells (Landi et al., SITC 2016). These HER2-CAR/PD-1-fusion T-cells exhibited improved effector functions and tumor activity. Subsequent evaluation of this hybrid system using confocal microscopy revealed decreased recruitment of SHP2 and decreased negative microcluster formation. This is in line with the known role of SHP2 in multiple co-inhibitory signaling pathways (PD-1, CTLA-4, BTLA, LAG3). Thus, SHP2 antagonism may ameliorate the tumor-induced functional exhaustion of CAR T-cells. The CRISPRScan online tool was used to identify potential CRISPR/Cas9 target sequences within the PTPN11 (SHP2-encoding gene) exon sequence and design corresponding oligonucleotides. Target sequences with the least number of predicted off-target events were selected based on two published algorithms. The microhomology-based CRISPRScan online tool was used to determine the target sequences with high likelihood of creating out-of-frame insertions/deletions at the CRISPR/Cas9 cleavage site via the error-prone non-homologous end joining. The oligonucleotides encoding the 20 nucleotide target sequences were then incorporated into the gRNA scaffold derived from the PX458 plasmid (Addgene #48138) using a PCR-based method. The resulting DNA template was purified...
and in-vitro transcribed to synthesize the individual gRNAs. The resulting gRNAs were purified in preparation for their electroporation into T-cells ex vivo utilized, cell sorting, and generated second-generation CAR T-cells (CD28/ζ endodomain) with or without the PD1 fusion molecules. Results: We synthesized five gRNAs targeting distinct TPN11 exons that are involved in SHP2 localization and enzymatic activity. The purified gRNAs will be electroporated singly or in pairs into HER2-CAR only and HER2-CAR/ PD-1 fusion for comparative functional evaluation of gMNPs. Conclusions: SHP2-2 knockout may facilitate targeting multiple inhibitory pathways to counteract tumor-induced exhaustion of CAR T-cells and improve their anti-tumor activity. Our methodology will also allow us to investigate the fundamental mechanisms of CAR-mediated signaling and their effect on T-cell function.

264  
CPRIT Grantee Poster Session A  
Size-Dependent Heating of Magnetic Iron Oxide Nanoparticles  
Sheng Tong, Rice University; G. Bao

Introduction: Magnetic iron oxide nanoparticles (MIONs) have great potential as an effective clinical thermal modality in cancer hyperthermia, thermoablation therapy, and controlled drug delivery. Upon exposure to an alternating magnetic field (AMF), MION can convert magnetic energy into thermal energy. The efficiency of energy conversion, i.e., heating efficiency, is determined by the magnetic relaxation of MIONs with respect to the AMF. A major challenge for the clinical applications of MION-based heat induction is the low heating efficiency of commercially available MIONs. To this end, we investigated the heating of superparamagnetic and ferromagnetic MIONs in a set of clinically relevant AMF. Experimental measurements of the magnetic properties and the heating efficiency of MIONs were compared with theoretical analysis based on a dynamic hysteresis model to gain insight into the mechanisms leading to efficient heat induction. Methods: Magnetite nanocrystals were synthesized by thermal decomposition of iron acetylacetonate. The DC and AC susceptibilities of the nanocrystals were measured using a superconducting quantum interference device (SQUID). Water-dispersible MIONs were obtained by coating the nanocrystals with DSPE-PEG copolymers using a dual solvent exchange method. For heat induction measurements, MIONs were exposed to an AMF generated with an inductive coil for 90 seconds under close-to-adiabatic conditions. The specific absorption rate (SAR) SAR was calculated from the temperature slope. Numerical analysis of the heat induction was performed with a Matlab program developed in the lab. Results: 8 batches of uniform magnetite nanocrystals were synthesized with the average size increasing from 6 to 40 nm. The nanocrystals from 6 to 19 nm exhibited typical superparamagnetic and ferromagnetic properties respectively in the room temperature micro hysteresis. MIONs with large sizes (> 19 nm) have significantly higher specific absorption rate (SAR) than that predicted by the widely used linear theory of magnetic fluid heating. The heating efficiency of MIONs in both superparamagnetic and ferromagnetic regimes increased with decreasing size, which can be accurately characterized with a modified dynamic hysteresis model. The 40 nm ferromagnetic nanoparticles have an SAR value approaching the theoretical limit under a clinically relevant AMF. An in vivo study further demonstrated that the 40 nm MIONs could effectively heat tumor tissues at a minimal dose. Conclusions: The study demonstrates the size-dependence of superparamagnetic and ferromagnetic iron oxide nanoparticles in clinically relevant AMF and provides the guidance for implementing clinical thermal therapies with minimal AMF exposure and optimal dosage of MIONs.

265  
CPRIT Grantee Poster Session B  
Designing realistic microfluidics devices for modeling microvascular flow  
Jiaming Guo, University of Houston; P. Ruchhoft; J. Slater; D. Mayerich

Introduction: Realistic models of microvascular networks are important for understanding tissue structure and function. This is particularly true in tissue samples, such as tumors, that are highly vascularized and unstructured. Since a strong microvascular component is seen in many diseases, there is an unmet need for microvascular models that accurately portray what occurs in vivo during normal tissue development and disease progression. Advances in microfabrication technology allow imaging microvessels and modeling them in hydrogels have opened the door to analyzing microvascular flow and behavior in developing or diseased tissue. Methods: We first collect a three-dimensional image of a mouse brain microvascular system at sub-micrometer resolution using SimScale and COMSOL Multiphysics v5.3 software. We start from 2D models for a better visualization and then 3D models for more practical demonstrations. The CFD simulation results match our simulation results in predicting flow directions. It also demonstrates that we can control the microvascular network imaged using FEM. The quantitative comparison demonstrates that the proposed simulation method succeeds in computing the velocity and pressure field across the whole network.

Conclusions: In this project, we develop software for simulating and visualizing flow in microvascular networks. We’ve demonstrated that our microvascular model has a high level of flow predictive capability based on comprehensive CFD models. This opens the door to creating realistic microfluidics models of microvascular flow representative of any sample network imaged with sufficient resolution. This can be used to study nutrient diffusion within developing tumors, as well as the behavior of cancer metastases within localized regions or normal tissue.
and negligible binding response for dFCrN at pH 7.4. In order to detect the weak binding activities of antibody variants to FCrN at physiological pH 7.4, SPR experiments with three different densities of scFcRn, 500 RU (low density), 2,000 RU (medium density), 4,000 RU (high density), were performed. DLS showed a non-detectable response to high density scFcRn as well as WT. DLS also showed equivalent antibody-dependent cellular cytotoxicity (ADCC) by PBMC and antibody-dependent cellular phagocytosis (ADCP) by M1-macrophage cell lines. Results: Clonogenic survival data showed the variation of RBE as a function of LET. From the entrance to Bragg peak the proton RBE increases slowly from 1.0 to 1.3 at the surviving fraction of 0.1, corresponding to the LET from 0.9 to 10.6 keV/µm. In the distal edge, the RBE increases sharply from 1.5 to 2.9 at the LET from 12.1 to 18.0 keV/µm. The foci data of 53BP1 were normalized to obtain the average number of foci per nucleus per ionization at different time points post-irradiation. For column #1 in the entrance area of a Bragg curve, the spatial ionization density is 42.0 per incident proton per micron, and the average number of foci per nucleus per ionization is 1.5E-6 ± 1.2E-6 at 24 hours post irradiation. For column #7 at Bragg peak, the corresponding values are 335.7 and 4.58E-6 ± 1.2E-6. For column #12 in the distal edge of a Bragg curve, the values are 543.4 and 1.31E-11 ± 3.55E-12. Conclusions: The clonogenic survival data show a non-linear relationship between proton RBE and LET. The foci data of 53BP1 show that DNA damage has a strong dependence on the spatial ionization density and increases in a non-linear trend as well.

268  Poster Session A
Pre-Clinical Evaluation of Cinobufotin as a Potential Anti-Ovarian Cancer Agent  Syeda Afroze, Texas A&M University System Health Science Center; A. McDowell; D. Dean; S. Henderson; V. Speights; T. McCormick; T. Kuehi; M. Uddin
Introduction: Cinobufotin (CINO), a cardiotonic steroid (CTS) or bufadienolide, is extracted from the skin secretions of the traditional Chinese medicine giant toads (Chan su). Recently it has been demonstrated that CINO inhibits lung and ovarian cancer cell function. In this study, we evaluated the effect of Cinobufotin by which it inhibits ovarian cancer cell function by utilizing three ovarian cancer cell; SK-OV-3, CRL-1978 and CRL-11731. We also performed CRL1978 xenograft model in nude mice and evaluated whether CINO inhibits the tumor growth. Methods: Each Cell lines were treated with different concentrations of CINO (0.1, 1, 5 and 10 µM). For each line cell proliferation, migration and invasion were measured by using a CellTiter Assay (Promega), Cytoselect Assay (Cell Biologs) and by using a FlouroBlock Assay (BD) respectively. Proliferating Cell Nuclear Antigen (PCNA) was also evaluated in cell lysates of CINO treated these 3 ovarian cancer cells by western blot analysis. Cell Cycle arrest and Cell viability were determined by fluorescence-activated cell sorting (FACS) analysis. We also performed Annexin V staining on CINO treated these 3 ovarian cancer cell lines by immunofluorescence to evaluate the pro-apoptotic protein expression and mitochondrial membrane potential (MMP) has also been measured using MMP kit utilizing FACS analysis. Male nu/nu mice were injected with CRL-1978 cells. When tumor volumes are measured at approximately 200–300 mm³, treatment with CINO was initiated. Upon completion of treatment mice were monitored for up to a week before euthanasia, xenografts were excised, then measured, weighed, and preserved. The sections were observed by microscopic examination. Results: Concentration of CINO at 0.5µM inhibit SK-OV-3, CRL-1978, and CRL-11731 cells proliferation, migration and invasion without cell death and loss of cell viability. Each cell lines differ in response to CINO, but SK-OV-3 had a stronger pro-apoptotic response compared to CRL-1978 and CRL-11731. A statistically significant decrease (p<0.05) in tumor size was observed after treatment with both 1 and 5 mg/kg concentrations of CINO when compared to vehicle. Conclusions: CINO is cell specific, as each cancer cell line responds differently. These data demonstrate that the mode of action of CINO is different on these 3 types of ovarian cancer cells. Treatment with Cinobufotin inhibits the growth of Clear cell ovarian cancer cell line CRL-1978. This model is a valid testing platform for additional tumor cell cultures.

269  Poster Session B
The correlation of biological effects and physical parameters in proton therapy  Fada Guan, The University of Texas M.D. Anderson Cancer Center; L. Bronk; M. Kerr; D. Ma; X. Wang; N. Sahoo; R. Mohan; D. Grossman
Introduction: The relative biological effectiveness (RBE) of protons to reference photons currently used in clinic is assumed to be 1.1, regardless of physical characteristics of proton beams and target cell types. However, recent biological experiments have indicated the spatial variability of RBE. Therefore, it is imperative to find the correlation of biological effects with physical characteristics in proton therapy. The knowledge gained from this line of study will facilitate the introduction of biologically-optimized proton therapy into the clinic to increase the therapeutic index. Methods: We have designed a versatile irradiation system to investigate the biological effects of protons with different physical parameters along a pristine Bragg curve. We used an 81.4 MeV/c scanning proton beam to irradiate H460 lung cancer cells cultured in 96-well plates. Two sets of cell irradiation experiments have been performed: the clonogenic survival experiments and the DNA double-strand break (DSB) induction (quantifying the established DSB marker 53BP1) versus the spatial ionization density. We used Monte Carlo toolkit Geant4 to calculate the dose and LET in cell layers. We used the track-structure Monte Carlo package Geant4-DNA to model the detailed interactions (ionization and excitations, etc.) of particles with cell layers. Results: Clonogenic survival data showed the variation of RBE as a function of LET. From the entrance to Bragg peak the proton RBE increases slowly from 1.0 to 1.3 at the surviving fraction of 0.1, corresponding to the LET from 0.9 to 10.6 keV/µm. In the distal edge, the RBE increases sharply from 1.5 to 2.9 at the LET from 12.1 to 18.0 keV/µm. The foci data of 53BP1 were normalized to obtain the average number of foci per nucleus per ionization at different time points post-irradiation. For column #1 in the entrance area of a Bragg curve, the spatial ionization density is 42.0 per incident proton per micron, and the average number of foci per nucleus per ionization is 1.5E-6 ± 1.2E-6 at 24 hours post irradiation. For column #7 at Bragg peak, the corresponding values are 335.7 and 4.58E-6 ± 1.2E-6. For column #12 in the distal edge of a Bragg curve, the values are 543.4 and 1.31E-11 ± 3.55E-12. Conclusions: The clonogenic survival data show a non-linear relationship between proton RBE and LET. The foci data of 53BP1 show that DNA damage has a strong dependence on the spatial ionization density and increases in a non-linear trend as well.

270  Poster Session A
Laser-induced Metallic Poly(Methyl Methacrylate) Nanoparticle: In vitro Biofluid Model to Evaluate Nanoparticle Design and in Vivo Biomolecule Interaction  Yelizaveta Avila, University of North Texas; D. Korii; D. Simmons; M. Omary
Introduction: Design, engineering, synthesis and characterization studies provide a suite of approaches to probe the use of nanoparticles (NP) in therapeutic applications, such as for targeting specific cancer cells. Near Infrared Nanoparticles (NIRM-NP) offer the window of opportunity to revolutionize cancer therapeutics, including thermal therapy. However, recent studies indicate that NP size matters and suggest that interacting biomolecules can change the designed size of these NPs by formation of a Protein Corona during NP transit to the target cell. This study evaluated for: 1) a Bioreduced AgPMMA NP as a platform to generate AgPMMA-NP. To mimic in vivo transit, an in vitro biomolecule fluid assay (BFA) model was developed, which used dispersion media of RPMI-1640 and/or fetal bovine serum. To capture Protein Corona physical effects on the design step synthesis product and final metallic-loading product, the Malvern Zetasizer was used to determine Dynamic Light Scattering (DLS) size distribution and zeta potential. To evaluate the Protein Corona effect on NP tumor cell killing, NP-cell interactions were screened for ATP production in the Promega-Cell-Titer-Glo cytotoxicity assay. Results: Time-course dispersion media analysis showed a NP product size increased in magnitude orders 10-100 fold, a fluctuating net charge (-) with zeta potential magnitude changes of 1-2 fold; Jurkat treated PMMA-NP alone or laser-PMMA treated tumor cells ATP levels are approximately equal to that of untreated tumor cells. AgPMMA-NP: Time exposure with different dispersion media revealed increased size, fluctuating net charge (-) and zeta potential changes 1-1.5 fold, treated NP alone or laser alone Jurkat tumor cells ATP levels approximated that of untreated tumor cells; however, combined laser-treatment reduced tumor live cells' ATP 25%. Conclusions: These preliminary studies suggest that laser-induced activation of AgPMMA-NPs that results in cell-killing of a Leukemia Jurkat clone. However, the biomolecular microenvironment forms a Protein Corona that affects size, stability, and net charge of designed nanoparticles. Characterization and evaluation studies using the BFA model could be used to refine NP design and synthesis protocols and improve tumor cell killing. Nevertheless, additional physical-chemistry BFA studies (e.g. shear affects, binding) related to nanoparticle-cell interaction are required to understand possible effects of the Protein Corona on tumor cell killing and thus the nanoparticle design.

271  Poster Session B
Interleukin-21 maintains CD62L expression during natural killer T cell ex vivo expansion and enhances antitumor activity of natural killer T cell therapy in vivo  Ho Ngai, Baylor College of Medicine; G. Tian; A. Courtney; E. Marinova; W. Huang; L. Guo; L. Metelitsa
Introduction: Valpha24-invariant natural killer T cells (NKTs) have potent antitumor properties and are being developed for cellular immunotherapy of cancer. Such therapy requires extensive ex vivo expansion of
272 Poster Session A

Palbociclib resistant breast cancer cells are sensitized to inhibition of DNA repair and cancer stem cell pathways
Nicole Kettner, The University of Texas M.D. Anderson Cancer Center; S. Vijayaraghavan; T. Bucu; D. Dupalli; K. Tripathy; K. Keyomarsi

Introduction: The CDK4/6 inhibitor palbociclib is currently being used in combination with endocrine therapy to treat advanced ER positive breast cancer patients. While this treatment has shown great promise in the clinic, about 25-35% of the patients do not respond initially, and almost all patients eventually acquire resistance. The precise biological mechanism(s) of the resistance to CDK4/6 inhibitors is still unknown and there are no independent biomarkers to predict response or resistance. Hence, understanding the mechanism(s) of acquired resistance to CDK4/6 inhibition is crucial to devise alternate treatment strategies.

Methods: We developed MCF7 and T47D resistant cells by treating them with escalating doses of palbociclib over a 8-month period. These cells not only are resistant to palbociclib, but cross resistant to the other CDK4/6 inhibitors; ribociclib and abemaciclib, suggesting common biochemical pathway block castrate-resistant prostate cancer cell growth. These cells not only are resistant to palbociclib, but cross resistant to the other CDK4/6 inhibitors; ribociclib and abemaciclib, suggesting common biochemical pathway block castrate-resistant prostate cancer cell growth.

Results: In comparison with the parental (sensitive) cells, these cells show decreased CSC population, colony formation and increased cell death via apoptosis. These cells not only are resistant to palbociclib, but cross resistant to the other CDK4/6 inhibitors; ribociclib and abemaciclib, suggesting common biochemical pathway block castrate-resistant prostate cancer cell growth. These cells not only are resistant to palbociclib, but cross resistant to the other CDK4/6 inhibitors; ribociclib and abemaciclib, suggesting common biochemical pathway block castrate-resistant prostate cancer cell growth. In addition, testing for synergy by treating cells with each compound in combination with irradiation revealed that combined treatment with olaparib and palbociclib significantly decreased CSC population, colony formation and increased cell death via apoptosis. These cells not only are resistant to palbociclib, but cross resistant to the other CDK4/6 inhibitors; ribociclib and abemaciclib, suggesting common biochemical pathway block castrate-resistant prostate cancer cell growth.

Conclusions: Our data suggests that combined treatment of two or more agents that are altered in the palbociclib resistant cells can provide a novel therapeutic strategy to combat CDK4/6 inhibitor resistance.

273 Poster Session B

Novel agents targeting a specific oxidative stress generating biochemical pathway block castrate-resistant prostate cancer cell growth
Hirak Basu, The University of Texas M.D. Anderson Cancer Center; G. Wu; I. Fokt; W. Priebe; G. Wilding; N. Wilganowski

Introduction: Castration-resistant prostate cancer (CRPC) is the second leading cause of cancer deaths among US men. Currently, a large number of small and low grade prostate cancers (PCa) are being diagnosed, only a few of them will metastasize and become lethal. A clinical method to distinguish aggressive from the indolent tumors is warranted. An enhanced glucose metabolism (Warburg effect) and invasion of cells from their organs of origin and metastasis to distant organs are two characteristics that are ubiquitous in most metastatic solid tumors including PCa. a glycine cleavage system ("moonlighting functions") of glycolytic enzymes have been investigated in relation to cancer cell invasion. We propose that antioxidative stressed PCa cells, as a countermeasure, redirect some of the glycolytic enzymes to their moonlighting functions. We have discovered a bio-chemical pathway of spermidine/spermine N1 acetyl transferase (SSAT) overexpression leading to polyamine oxidation as one major oxidative stress generating pathway in the PCa cells. We have developed targeted agents to block this pathway and thus prevent PCa progression to CRPC and metastatic CRPC (mCRPC).

Methods: We used a novel microfluidic device that separates the invading from the non-invading PCa cells based in a 3D collagen I matrix mimicking bone microenvironment. We performed ICC analysis of the separated cells for SSAT, glycolytic enzymes, GAPDH and F-actin levels. We also carried out proteomic analysis of GAPDH levels and its oxidation state and metabolomic analysis for enzymatic activities of SSAT and GAPDH. Results: PCa cells show minimum invasion, whereas between 30-40% of C4-2 cells invade into the matrix. ICC assay shows that most migratory C4-2 cells as well as PCa cells isolated from some patients prostate tissues overexpress SSAT, while stationary cells do not. Proteomic analysis shows that an over-expressed SSAT increases GA and F-actin expression in C4-2 cells. Our targeted agent markedly inhibits growth of the C4-2 cells both in culture as well as in vivo.

Conclusions: SSAT expression and a consequent increase in oxidative stress are related to invasion of CRPC. Oxidation of certain glycolytic enzymes is a hallmark of PCa cells derivative to their moonlighting functions related to cellular invasion and metastasis. These effects may be monitored in patient biopsies and/or prostatectomy tissues for PCa prognosis. Targeted agents can be developed for precision therapy of mCRPC patients dependent on this mechanism of metastasis.

274 Poster Session A

Screening for novel therapeutic agents for the treatment of aggressive childhood hepatoblastoma
Kristi George, The University of Texas Health Science Center at San Antonio; J. Peralba; M. Hart; H. Bansal; G. Tomlinson

Introduction: Hepatoblastoma is the most common malignant liver tumor in childhood. Pediatric patients, and their incidence has been rising annually over the past several decades. Despite improved survival outcomes, a subset of patients has more aggressive tumors which are refractory to conventional cisplatin therapy and surgery. We are focused on identifying novel compounds for the treatment of aggressive hepatoblastomas. In this research, we are screening for candidate drug compounds. We have identified four candidate drug compounds using RNA-seq analysis of the separated cells for SSAT, glycolytic enzymes, GAPDH and F-actin levels, which increased by >12-fold in the resistant cells. Further, treatment with a STAT-3 inhibitor, napabucasin significantly decreased the CSC population and mammosphere formation, indicating a crucial role for the IL-6/STAT-3 pathway in driving CSCs and palbociclib resistance. Since DNA repair pathways were previously shown to be important in palbociclib resistant cells, we examined their sensitivity to DNA damaging agents. Results showed that resistant cells were more sensitive to olaparib (PARP inhibitor), with no effect on CSCs. Next, we examined if combined treatment with agents targeting IL-6/STAT-3 and DNA repair pathways would be synergistic in palbociclib resistant cells. Palbociclib resistant cells were sensitized to cisplatin and napabucasin significantly decreased CSC population, colony formation and increased cell death via apoptosis, when compared to no-treatment or single treatment controls of the palbociclib resistant cells.

Conclusions: Our data suggests that combined treatment of two or more agents that are altered in the palbociclib resistant cells can provide a novel therapeutic strategy to combat CDK4/6 inhibitor resistance.

275 Poster Session B

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Hirak Basu, The University of Texas M.D. Anderson Cancer Center; G. Wu; I. Fokt; W. Priebe; G. Wilding; N. Wilganowski

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Methods: We used a novel microfluidic device that separates the invading from the non-invading PCa cells based in a 3D collagen I matrix mimicking bone microenvironment. We performed ICC analysis of the separated cells for SSAT, glycolytic enzymes, GAPDH and F-actin levels. We also carried out proteomic analysis of GAPDH levels and its oxidation state and metabolomic analysis for enzymatic activities of SSAT and GAPDH. Results: PCa cells show minimum invasion, whereas between 30-40% of C4-2 cells invade into the matrix. ICC assay shows that most migratory C4-2 cells as well as PCa cells isolated from some patients prostate tissues overexpress SSAT, while stationary cells do not. Proteomic analysis shows that an over-expressed SSAT increases GA and F-actin expression in C4-2 cells. Our targeted agent markedly inhibits growth of the C4-2 cells both in culture as well as in vivo.

Conclusions: SSAT expression and a consequent increase in oxidative stress are related to invasion of CRPC. Oxidation of certain glycolytic enzymes is a hallmark of PCa cells derivative to their moonlighting functions related to cellular invasion and metastasis. These effects may be monitored in patient biopsies and/or prostatectomy tissues for PCa prognosis. Targeted agents can be developed for precision therapy of mCRPC patients dependent on this mechanism of metastasis.

274 Poster Session A

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Conclusions: Our data suggests that combined treatment of two or more agents that are altered in the palbociclib resistant cells can provide a novel therapeutic strategy to combat CDK4/6 inhibitor resistance.
libraries and eighteen additional hits from the Chembridge Diverset and Maybridge Hitfinder libraries, which demonstrated cytotoxic activity against both cell lines. Conclusions: Despite improved outcomes in hepatoblastoma patients, there is still a significant number of patients who will succumb to their disease. As a result, it is critical that new treatments be identified to treat these aggressive tumors. High throughput screening offers an efficient and effective way to rapidly screen large libraries of compounds for potential cytotoxic activity against these tumors.

275 Poster Session B
Modelling Spread of Oncolytic Viruses in Heterogeneous Cell Populations
Hana Dobrovolny, Texas Christian University

Introduction: One of the most promising areas in current cancer research and treatment is the use of viruses to attack cancer cells. A number of oncolytic viruses have been identified and identified to date that possess the ability to destroy or neutralize cancer cells while infecting minimal damage upon healthy cells. Mathematical models that correctly describe the evolution of infected tumor systems are critical to the successful application of oncolytic virus therapy. Existing mathematical models are focused on the effects of virus infection on tumor cells, but do not consider possible spread of the virus to normal healthy cells. Methods: We have developed a mathematical model of oncolytic virus infections of tumors that includes both tumor cells and neighboring normal cells. We use mathematical analysis and computer simulation to examine the conditions which lead to eradication or control of oncolytic virus infections of tumors. Results: We find that differences in infection rate between the two cell types are necessary for eradication of tumors while leaving normal cells unharmed. Differences in production rate or infected cell lifespan are not sufficient to protect healthy cells from infection. Conclusions: Mathematical models can assist in the safe development of oncolytic viral therapy by identifying conditions that limit spread of the virus to non-cancerous cells.

276 Poster Session A
Metabolic adaptations establish immunotherapy resistance in melanomas
Ashvin Jaiswal, The University of Texas M.D. Anderson Cancer Center; S. Pudakalakatti; P. Dutta; A. Liu; T. Barthowiak; C. Ager; M. Davies; J. Allison; R. Davis; J. Wargo; P. Bhattacharya; D. Hong; M. Curran

Introduction: Despite the success of T cell checkpoint blockade antibodies in treating an array of cancers, the majority of patients still fail to respond to these therapies, or respond transiently and then relapse. The mechanisms which drive lack of response to checkpoint blockade, whether pre-existing or evolved on therapy, remain unclear. Methods: To address this critical gap in clinical knowledge, we established a mouse model of melanoma designed to elucidate the molecular mechanisms underlying immunotherapy resistance. Through multiple in vivo passages, we selected a B16 melanoma tumor line that evolved complete resistance to combination blockade of CTLA-4, PD-1, and PD-L1, which cures ~80% of mice of the parental tumor. Using gene expression analysis, proteomics, and immunogenomics, we determined the adaptations engaged by this melanoma to become completely checkpoint resistant. NMR spectroscopy, Seahorse XF Analysis, flow cytometry, confocal microscopy and western blot analysis provided further insight into the mechanisms driving checkpoint blockade resistance. Results: Acquisition of immunotherapy resistance by these melanomas was driven by coordinate upregulation of the glycolytic and aldo-ketoreductase pathways to create a metabolically hostile microenvironment in which T cell function is profoundly suppressed. When re-introduced into the parental tumor, the genes most closely associated with these metabolic adaptations confer enhanced immunotherapy resistance. We have validated upregulation of these pathways in a unique cohort of melanoma patients who failed dual checkpoint blockade. Additionally, we employed MRI imaging to visualize metabolic changes acquired by resistant tumors in live mice. Clinical application of this technique could provide a much-needed non-invasive tool to predict or reverse immunoevasive selectivity. Conclusions: Uprogulation of glycolytic metabolism and the aldo-ketoreductase pathway by melanoma tumor cells cripples T cells in the microenvironment and confers resistance to checkpoint blockade.

277 Poster Session B
Exfoliated single-cell genomics for assessing prostate cancer progression and treatment options
Chun-Lin Lin, The University of Texas Health Science Center at San Antonio; X. Tan; C. Lin; P. Osmuski; M. Liss; M. Chen; A. Chen; C. Wang; J. Liu; A. Horning; G. Huang; K. Mitsuya; Y. Wang; J. Taverna; K. Xu; V. Jin; Z. Lai; N. Kirmat; M. Gaczynska; C. Chen; T. Hoong

Introduction: Exfoliated prostate cancer cells undergoing epithelial-mesenchymal transition (EMT) may enter the bloodstream and invade organs for distant colonization. Different from primary tumor cells, these circulating tumor cells (CTCs) may exhibit unique biological properties, enabling their active intravasation and extravasation in the circulation. To date, there is limited information on genomic selection of tumor cells transitioning from active in situ proliferation to effective distant colonization. Here we constructed whole-genome copy number profiles on prostate single cells isolated from urine and blood for comparative genomic analysis of primary and disseminated tumor cells in a patient. Methods: With specific markers, we isolated 407 single prostate cells exfoliated in urine and blood of 19 patients or from two cancer cell lines. These single cells were subjected to multiple displacement amplification known to unbiasedly amplify a cell genome and confirmed by PCR analysis of a reference gene panel. Barcoded libraries prepared from amplicons were pooled for whole genome sequencing. On average 4 x 10^7 paired-end reads per cell were processed for genome mapping. From the 2X genome coverage, we calculated copy-number alterations (CNAs) at the 250 Kbs resolutions. Results: Clonal abnormalities of well-known oncogenes and tumor suppressors, including amplified MYC and deleted RB1, were common in prostate cells exfoliated in urine of advanced patients, but less frequent in indolent cancer patients. We further identified amplified regions harboring novel loci of which is linked to recurrent prostate cancers. Among these loci, amplified MEN1 and HSF1 known to promote castration resistance and EMT were frequently present in CTCs. Different from exfoliated tumor cells in urine, these CTCs exhibited biophysical phenotypes with high adhesion capability likely for vascular permeation and distant invasion. In vitro testing of CTCs revealed potential therapeutic targeting of these two amplified loci. Conclusions: This parallel genome analysis of exfoliated cells in both urine and blood opens the possibility of minimally invasive evaluation of disease progression and treatment options for a man with advanced prostate cancer.
ABSTRACTS
ACADEMIC RESEARCH

did not significantly increase EFS over tempo + irino alone. We developed a two color flow cytometry assay employing directly-labeled dinutuximab + dinutuximab di-antibody (DA) (neomycin-di-antibody) to identify tumor cells that enables quantifying GD2 expression in bone marrow aspirates. **Conclusions:** Our data with patient-derived NB cell lines and PDXs are consistent with a prior report and indicate that low GD2 expression can occur in NB and may be more frequent in PD patients. NB PDXs in particular were produced by a prediluted infection in a 384 well plate format when combined with chemotherapy. Dinutuximab enhanced activity of temozolomide + irinotecan in a NB PDX with high-GD2 expression but not in a NB PDX with low GD2. Quantifying GD2 expression in NB is a potential biomarker of activity that warrants evaluation in patients treated with dinutuximab combined with temozolomide + irinotecan. 280

**Poster Session A**
**Robust Anti-Tumor Immunity is Transient and Limited by Immune Escape in a Novel Model of HPV-Associated Head and Neck Cancer**

J. J. Mooney; A. Sikora; S. Young

Introduction: More than 65,000 men and women will develop head and neck squamous cell cancer (HNSCC) this year in the US alone and it accounts for 4% of all cancers in the United States. Given the well-known co-morbidities and recurrence rates associated with conventional treatment, there remains a real need for innovative new approaches to treating both human papilloma virus (HPV)-related and non-HPV related HNSCC. Immune checkpoint inhibitors have been the most successful cancer immunotherapy approach thus far, although they are only effective in up to 20% of patients. The identification of HNSCC patients who might benefit from immunotherapy can be overcome by biomaterial-based combinatorial therapies to treat HNSCC. Herein, we describe a novel preclinical mouse model for immunologic targeting of HPV-related HNSCC to investigate the efficacy of an injectable therapeutic cancer vaccine. **Methods:** MOC2-E6E7 is an HPV 16 E6E7 expressing cell line transduced with the c-Myc and MDM2 oncogenes. E6E7 proteins E6 and E7, was generated by retroviral transduction of HPV16 E6E7 in parental MOC2 cells obtained from the Uppaluri lab, Harvard University. Orthotopic tumors in mice were established by intra-or cochlear inoculation of MOC2-E6E7 cells for our studies. We used mesoporous silica rod (MSR)-based vaccines to examine efficacy of an injectable therapeutic cancer vaccine system. MSR-vaccines loaded with bioactive reagents (recombinant murine GM-CSF, CpG-ODN, and E7 long peptide or tumor lysate), were injected subcutaneously in the bilateral flanks of mice that were previously inoculated with MOC2-E6E7. Several independent approaches were used to determine efficacy, expression of E6E7, and immune profile expression. **Results:** In vivo tumor growth kinetics reveal that MOC2-E6E7 tumors had delayed growth in immunocompetent mice when compared to parental MOC2 tumors. In contrast, MOC2-E6E7 tumor growth rate was similar to MOC2 in immunocompromised mice. By flow cytometry and multiplex imaging, we determined MOC-2-E6E7 tumors have a T-cell inflamed phenotype. Efficacy studies with a MSR-based vaccine showed slowed MOC2-E6E7 tumor growth and increased survival. **Conclusions:** We developed a syngeneic murine model of HPV-related HNSCC, MOC2-E6E7 which expresses well-defined tumor specific antigens that can be targeted by the vaccine system. The effectiveness of loss of E6 and E7 expression led to escape of resistant tumor cells from immune control, causing a delayed tumor growth phenotype in this model. Additionally, MSR-based vaccines show promise in delaying tumor growth and increase median survival time in HPV-related HNSCC. Future studies will explore the efficacy of MSR-based vaccines in combination with other immunotherapy modalities.

281

**Poster Session B**
Development of a robust high throughput luminescent assay for lysyl hydroxylase (LH2)

Ashwini Devkota; The University of Texas at Austin; J. Veloria; H. Guo; J. Kunre; E. Cho; K. Dalby

**Introduction:** Lysyl hydroxylase-2 (LH2), an Fe(II) and alpha-ketoglutarate (α-KG) dependent oxygenase, catalyzes the hydroxylation of telopeptide lysine residues on collagen, leading to the formation of stable collagen cross-links. By promoting accumulation and stabilization of hydroxylysine alpha-derived collagen cross-links (HLCCs) in fibroblast and various other tissues, LH2 is believed to cause fibrotic diseases, and enhance progression and metastasis of various cancer types such as lung cancer, breast cancer and sarcoma. Therefore, LH2 is a potential therapeutic target for fibrotic diseases and cancer. Identification of small molecule inhibitors for the treatment of these diseases is essential. This study describes a liquid handling system that is amenable to high throughput screening. Currently, no such assays are available for LH2. Therefore the purpose of our research was to develop a robust bioluminescence-based high throughput assay that can facilitate the identification of potent, specific small molecule inhibitors of LH2. **Methods:** Chinese hamster ovary cell-derived LH2 and collagen helical substrate (IKGIKGIKGK) were used for the assay. Enzyme concentration, substrate concentrations and reaction times were optimized to maximize signal to background ratio while being within the linear range of the Z′ factor. A novel bioluminescence-based high throughput assay was used to convert succinate product to luminiscence signal. Assays were miniaturized to a 10 µL volume in a 384 well plate format. The robustness of the assay was further tested and validated in a screen of 65,000 compounds. **Results:** The assay was sensitive enough to detect luciferase that was produced by a luciferase reporter gene in a 384 well plate format. The optimized assay demonstrated a 15-20 fold higher signal compared to the background. The average 2 for the screen was above 0.8, suggesting high confidence in the identified hits. A 3.8% hit rate was obtained from the primary screen of 65,000 compounds (compound screening rate of 50% inhibition was considered a hit). Top 1000 hits from primary screen were further confirmed in a secondary screen using the same assay and ultimately in a dose response assay to determine the potency. The screen identified several specific hits with potency in the low nanomolar to low micromolar range. **Conclusions:** Overall, the assay was shown to be robust and has the potential to screen large number of small molecule libraries. The assay will facilitate screening of larger libraries for identifying potent, specific small molecule inhibitors for LH2.

282

**Poster Session A**
A novel LC-MS/MS assay using pH gradient for quantification of underivatized polyamines in cancer cells

Hwanjung Cho; Texas Tech University Health Sciences Center; D. Verlekar; M. Kang

**Introduction:** Altered levels of polyamines in biological specimens have been suggested to be potential biomarkers of cancer. Difluoromethylornithine (DFMO, an irreversible inhibitor of ornithine decarboxylase), a modulator of polyamine levels has shown anticancer activity in vitro and in vivo, and an anticancer clinical trial is being conducted to evaluate DFMO in neuroblastoma. In order to determine the role of DFMO in the cytotoxic activity against neuroblastoma cells it is necessary to accurately measure the changes in polyamines in the cells. Existing analytical methods include a use of derivatization with ion-pair reagents to improve the sensitivity of the determination. However, these methods may cause incomplete reactions, contamination, and signal suppression as well as they are time consuming. In this study, we present a novel pH gradient method for the quantification of polyamines (putrescine, spermidine and spermine) in cancer cells. **Methods:** To separate polyamines and basic amines under the conventional reversed-phase conditions, a multi-column composed of C18 and weak ionic ligands was adopted. The pH gradient was generated from pH 5.3 to pH 2.5 with 2 mM ammonium acetate and 0.4% acetic acid in 10% acetonitrile as mobile phase. The detection of polyamines was performed using multiple reaction monitoring on electrospray ionization mass spectrometry operated in the positive ion mode. The developed method was validated according to the FDA guidance on bioanalytical method validation. Polyamines levels were measured using the developed method for NB cells treated and non-treated with DFMO. **Results:** A pH gradient method increased resolution and sensitivity of polyamine determination. By LC-MS/MS analysis of multiplexed samples, MOC2-E6E7 tumors have a T-cell inflamed phenotype. Efficacy studies with a MSR-based vaccine showed slowed MOC2-E6E7 tumor growth and increased survival. **Conclusions:** We developed a syngeneic murine model of HPV-related HNSCC, MOC2-E6E7 which expresses well-defined tumor specific antigens that can be targeted by the vaccine system. The effectiveness of loss of E6 and E7 expression led to escape of resistant tumor cells from immune control, causing a delayed tumor growth phenotype in this model. Additionally, MSR-based vaccines show promise in delaying tumor growth and increase median survival time in HPV-related HNSCC. Future studies will explore the efficacy of MSR-based vaccines in combination with other immunotherapy modalities.

283

**Poster Session B**
Microfluidic cell isolation technology for drug testing of single tumor cells and their clusters

Swastika Bithi; Texas Tech University; S. Vanapalli

**Introduction:** There is a growing interest in conducting drug screens with primary cells derived from human tissues and biofluids to predict patient outcomes. These primary cells contain inherent heterogeneity of cancer that demands single-cell analysis. In contrast to immortalized cell lines, primary cells are a scarce resource and yet preclinical studies demand diverse assays probing specific targets, off-targets and cytotoxicity. Drug access with patient-cell line or circulating tumor cells requires manipulating small sample volumes without loss of rare disease-causing cells. **Methods:** Here, we report an effective technology for isolating and analyzing individual tumor cells and their clusters from minute sample volumes using an optimized microfluidic device integrated with pipettes. The method involves using microfluidic pipetting to create an array of cell-laden nanoliter-sized droplets immobilized in a microfluidic device without

ACADEMIC RESEARCH

ABSTRACTS

103

ACADEMIC RESEARCH

ABSTRACTS
loss of tumor cells during the pipetting process. Results: Using this technology, we demonstrate single-cell analysis of tumor cell response to the chemotherapy drug doxorubicin. We find that even though individual tumor cells display diverse uptake profiles of the drug, the onset of apoptosis is determined by accumulation of a critical intracellular concentration of doxorubicin. Experiments with clusters of tumor cells compartmentalized in microfluidic drops reveal that cells within a cluster have higher intracellular levels of doxorubicin than cells alone. This result suggests that circulating tumor cell clusters might be able to better survive chemotherapy drug treatment. Conclusions: Our technology is a promising tool for understanding tumor-cell-drug interactions in patient-derived samples including rare cells.

284
Title: Poster Session A
Synergistic Activity of Fenretidine (4-HPR) and the BCL-2 Inhibitor ABT-199 in Human Neuroblastoma Preclinical Models
Authors: Thin Nguyen, Texas Tech University Health Sciences Center; B. Koneru; S. Wei; M. Makena; W. Chen; E. Urias; M. Kang; C. Reynolds

Introduction: Despite current intensive treatment with chemotherapy and radiation, ~35% of neuroblastoma patients still die of the disease. Fenretidine (4-HPR), a synthetic retinoid formulated as an oral powder in Lym-X-Sorb (4-HPR LXS), has shown multiple complete responses and encouraging event-free survival in a phase 1 neuroblastoma clinical trial. Anti-apoptotic BCL-2 family of proteins play critical roles in neuroblastoma cell survival, which is linked with BCL-2 dependent BCL-, a common feature in NB cell lines. Synergistic activity of fenretidine and the pan-BCL-2 family inhibitor ABT-737 (clinical version, ABT-263) has been demonstrated in neuroblastoma preclinical models, but ABT-263-associated thrombocytopenia led to development of ABT-199, a BCL-2 specific inhibitor that has achieved an FDA approved indication for chronic lymphocytic leukemia. The purpose of the current study is to investigate the preclinical activity of ABT-199 in combination with 4-HPR activity in BCL-2-dependent neuroblastomas.

Methods: Cytotoxicity was assessed by combining ABT-199 (0-10 mM) with 4-HPR (0-10 mM) using DIMSCAN, synergy by combination index, and apoptosis by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Protein expression was determined by western blot. Gene expression manipulations were conducted with lentiviral induction. Results: Cytotoxic synergy was observed between 4-HPR and ABT-199 in 18 out of 20 tested NB cell lines in vitro, 4-HPR + ABT-199 induced greater apoptosis than single agents. BCL-2 protein expression was significantly higher in cell lines with the highest sensitivity to ABT-199 (p<0.05). The synergy of the combination was greater in NB cell lines that are highly sensitive to ABT-199 as a single agent compared with ones that are relatively resistant to ABT-199. 4-HPR + ABT-199 + Keto (as a CYP3A4 inhibitor used to increase 4-HPR plasma concentration) significantly (p<0.0001) improved the event-free survival (EFS) of mice relative to single agents in a patient-derived xenograft (PDX) model with high-BCL-2 established from progressive disease (PB-D67). ABT-199 improved EFS of 4-HPR + ABT-199 + Keto group = 93 days versus 43 days for 4-HPR + Keto and 46 days for ABT-199 + Keto. 4-HPR + ABT-199 + Keto did not improve EFS of mice versus single agents in a low-BCL-2 PDx model. 4-HPR showed significant induction of NOXA protein expression, NOXA knockdown abrogated synergistic cytotoxicity of 4-HPR + ABT-199, and overexpression of NOXA sensitized NB cell lines to single agent ABT-199. Conclusions: Induction of NOXA by 4-HPR mediates synergistic cytotoxicity of 4-HPR + ABT-199 for neuroblastoma.

285
Title: Poster Session B
Selective delivery of potent anticancer agents facilitated by hypoxia mediated cleavage of corresponding prodrug conjugates
Authors: Zhe Shi, Winters; E. Zhe Shi, W. K. Devkota; Y. Wang; J. Anton Naumov, Texas Christian University; E. Zhe Shi, W. K. Devkota; Y. Wang; J. Anton Naumov

Introduction: Small molecules such as paclitaxel, vinblastine, and monomethyl auristatin E that interfere with the tubulin-microtubule protein system are clinically relevant anticancer agents. The natural products colchicine, combretastatin A-4 (CA4), and combretastatin A-1 (CA1) are potent inhibitors of tubulin polymerization that have inspired the discovery of several small-molecule inhibitors of tubulin polymerization (KGP03 and KGP18 are representative) that bind to the colchicine site on tubulin and demonstrate profound cytotoxicity (low nM to pM) against human cancer cell lines. Tumor associated hypoxia provides an unique opportunity for targeted therapy through selective reductase enzyme-mediated release of highly potent anticancer agents from bioreductively activatable prodrug conjugates (BAPCs).

Methods: A series of substituted nitrothiophene, nitrofuran, and/or nitromidazole-triggered BAPCs that incorporate CA1, phenthiophen, KGP03, KGP18, and CA4 (for reference comparison) were synthesized, and evaluated in the following assays: (1) cleavage under anoxic conditions by the reductase enzyme, NADPH cytochrome c P450 oxidoreductase (POR), that is implicated in the bioreductive cleavage of compounds with nitrothiophene and nitroimidazole triggers, and (2) differential cytotoxicity under hypoxic versus normoxic conditions in cancer cell lines with the established bioreductive compound tirapazamine (TPZ) as the control. Results: The CA4-gem-dimethylthiophenothiazine BAPC (KGP372) proved exemplary in comparison to its nor-methyl and mono-methyl congeners. It was stable in phosphate buffer (pH 7.4, 24 h), cleaved by POR, was inactive (desirable for activation in tumor) as an inhibitor of tubulin polymerization (IC50 > 20 μM), and demonstrated hypoxia-selective activation in the A549 cell line [hypoxia cytotoxicity ratio (HCR) = 40]. The monomethyl nitroimidazole BAPCs of KGP03 and KGP18 produced positive HCRs in these initial assays, and the gem-dimethyl and nitrofuran phenstatin BAPCs underwent efficient POR-mediated cleavage. In a preliminary in vivo dynamic bioluminescence imaging (BLI) study, KGP372 (dosed at 180 mg/kg) induced a decrease in light emission in two of three tumors within 4 h in an orthotopic 4T1 syngeneic mouse breast cancer model. This is potentially indicative of in vivo cleavage by POR and subsequent vascular disruption by the released CA4. The related CA1-gem-dimethylthiophenothiazine BAPC (KGP461) was also promising (HCR = 12) and demonstrated cleavage upon treatment with POR. However, KGP461 was not stable to long exposures (24 h) in phosphate buffer (pH 7.4), suggesting that pharmacokinetic (PK) considerations may prove crucial for the successful future development of these (and related) BAPCs as therapeutic agents.

Conclusions: The gem-dimethyl BAPCs were the most promising from this series and warrant further evaluation and development.

286
Title: Poster Session A
Graphene Oxide Vehicles for Molecular Imaging and Cancer Detection
Authors: Anton Naumov, Texas Christian University; E. Zhe Shi, W. K. Devkota; Y. Wang; J. Anton Naumov

Introduction: In order to address adaptability and variability of multiple cancer types, novel transformative approaches to cancer treatment imaging and detection are required. A new interdisciplinary field of nanomedicine provides effective routes for cancer prevention, detection and treatment through remarkable properties of novel nanomaterials. One of those graphene has only started finding its applications in biotechnology. In this work we explore the properties of its functional derivative, graphene oxide (GO), that can confer new features of GO utilized for imaging and cancer detection. Unlike many carbon nanomaterials, GO is water soluble and exhibits fluorescence over the functionalization-induced band gap. A large graphene platform with oxygen containing groups that can be easily functionalized with active agents or analyze binding sites makes GO attractive for biosensing and drug delivery applications. In addition, an intrinsic GO fluorescence in red/near-infrared region with reduced biological autofluorescence background provides a possibility of fluorescence imaging without the need in additional fluorophores.

Methods: We explore these properties to develop a multifunctional delivery/molecular imaging/sensing platform. GO utilized in our work shows little to no apparent cytotoxicity in concentrations of up to 15 mg/mL. We optimize the size of the commercially available GO flakes via ultrasonic processing for the most efficient cellular internalization and use spectrally-resolved fluorescence imaging for in vivo detection in the spectral range specific to GO fluorescence emission. Furthermore, ozone processing adding extra oxygen-containing functional groups to GO surface is used to spectrally adjust GO emission and enhance its intensity. Concomitantly, such processing provides the basis for versatile coherent functionalization of anticancer agents to the addends on GO platform via synthetic route akin to peptide synthesis. Results: Optimized GO moieties show efficient intracellular accumulation at 1h after transfection in both cancer (MCF-7, HeLa) and healthy (HEK-293) cells and clearance through 24h post transfection. A pH dependence of GO emission discovered in our previous work provides a sensing mechanism for the advent of tumor environment of cancer cells. In this regard, spectrally-resolved fluorescence microscopy imaging confirms enhancement of red GO emission features and of GO fluorescence in green in cancer versus healthy cell environments.

Conclusions: As a result we propose GO as efficient multifunctional candidate for delivery of active agents, fluorescence sensing and of cancerous environments in vitro, ex vivo and intravitaly.

287
Title: Poster Session B
Systemic depletion of serum methionine by engineered methioninase for cancer therapeutics
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Introduction: In cancer biology research, it has been found that cancer cells exhibit altered metabolism compared to normal cells and it has been shown that some types of cancer cells are far more sensitive than normal cells to methionine starvation. Past studies have shown that methionine-dependent tumor cells are not able to survive if the

ABSTRACTS
serum methionine is decreased to ≤ 5µM. We engineered human cystathionine gamma-lyase to accept methionine as a substrate and have it isolated to > 95% purity as a recombinant protein (hMETase) variant with high activity to systematically deplete of serum methionine. The engineered Methioninase was then tested in vitro and in vivo for effects on cell survival, cell cycle arrest, generation of reactive oxygen species (ROS), Western blotting and tumor growth inhibition. Methods: We engineered and characterized several variants of human cystathionine gamma-lyase (hMETase) for catalytic activity, thermostability, pharmacokinetics and pharmacodynamics. The enzyme was also tested in cultures of prostate cancer (PCa) cells for effects on cell survival by crystal violet assay, cell cycle analysis by PI staining, measurement of glutathione and ROS and Western blotting for cell signaling changes. Allograft and xenograft studies were performed to assess the inhibition of PCa tumor growth in vivo using pharmacologically optimized hMETase. Results: The best variant, hMETase V8.4 isolated from phylogenetic library showed a 10-fold better kM/Ki values (0.59 to 3.5 s M−1) in degrading methionine and also greater stability in thermal melting analyses compared to our previous version of variant, hMETase V3.1. In pharmacokinetics analyses, its half-life is~39 hours and furthermore, it efficiently lowered serum methionine concentration from 113 µM to 17 µM in 48 hours without the requirement of a methionine restricted diet (one dose: 50 mg/kg). Treatment with this enzyme selectively induced cell cycle arrest and death in PCa cells, depletion of intracellular GSH and elevation of ROS. Methioninase suppressed the growth of PCa allografts (mouse PCa cells) and xenografts (human PCa cells) with no apparent signs of toxicity. Mechanistically, Methioninase treatment caused activation of AMPK signaling, leading to mTORC1 inhibition and induced formation of LC3 II indicating induction of autophagy. Conclusions: The hMETase V8.4 efficiently lowered serum methionine concentration in pharmacodynamic analyses, suppressed the growth of PCa cells both in vitro and in vivo, and was very well tolerated. These results suggest that Methioninase represents a potentially safe and effective therapeutic modality for the treatment of prostate and possibly other cancers.
ABSTRACTS

291 Poster Session B

Initial ex-vivo clinical validation of a dendritic cell-targeting therapeutic HPV vaccine for patients with HPV-related cancers

Falguni Parikh, Baylor College of Medicine; J. Quintana; S. Kang; Q. Yong; L. Wang; J. Patel; B. Kane; S. Oh; J. Woo; E. Chiao; A. Sikora

Introduction: HPV-related immunosuppression puts patients at increased risk of HPV-related cancers (HPVCA) of the cervix, oropharynx, and anus. Therapeutic vaccination is one approach to treatment of HPV-related cancers; while little is known about the ability of HPV-positive patients to respond to therapeutic cancer vaccines, it is possible that highly immunologically active agents will be required to reverse persistent T cell defects. One such immunotherapeutic approach is the combination of CD40HVac, a novel therapeutic HPV vaccine comprised of the full-length CD40 ligand conjugated to a monoclonal antibody to CD40, with a toll-like receptor (TLR) agonist to boost innate immunity. Preclinical data suggests that CD40HV ac is highly immunogenic and capable of eliciting E6+ E7+ T cell responses. The immunogenicity of CD40HV ac is further enhanced by delivering a potential adjuvant, a TLR agonist, to the same dendritic cells targeted with CD40HV ac. The goal of this study is to accelerate the application of therapeutic HPV vaccines in HIV/HPV co-infected patients, by determining the preliminary immunogenicity of CD40HVac and TLR agonist conjugated CD40HVac in peripheral blood mononuclear cells (PBMC) collected from HIV-positive HPVCA patients. Our ultimate goal, once immunogenicity of the conjugates is determined for HIV-negative donors, is to test the vaccine in HIV+ patient samples.

Methods: CD40HVac fusion protein was produced with a CHO cell line and conjugated to novel candidate TLR7 agonists to create CD40HVac#1, CD40HVac#7, CD40HVac#20, and CD40HVac#32. CD40HVac#1-7 ligand conjugates were tested for their binding to human antigen presenting cells, including DCs, and for their ability to activate cells via TLR7 using TLR7 reporter cell assay. Immunogenicity of the vaccine was tested by determining IFN-γ production from proliferation of CD4+ and CD8+ T cells in PBMC isolated from HIV-negative HPV+ oropharyngeal cancer patients using an IFN-g ELISPOT assay.

Results: All CD40HVac#7 ligand conjugates were able to bind to human antigen presenting cells. Additionally, CD40HVac#1-7 ligand conjugates were also confirmed to activate cells via TLR7. All the conjugates were capable of inducing HPV-specific IFN-γ production. ELISPOT assay confirmed that the CD40HVac#1-7 ligand conjugates down-regulated the expression of pro-angiogenic, vascular endothelial growth factor (VEGF), IL-10, and anti-hypoxic proteins, VEGF, HIF1alpha, and chemokine receptor 4 (CXCR4) was measured by western blotting using GAPDH as loading control. The dose response curves from 3-4 independent experiments with triplicates were plotted. EC50 and statistical significance were calculated using Prism Graph Pad 6.0 version. Results suggest that the tested analogs dose-dependently decreased cell viability and inhibited cell proliferation in the order #32> #20> #7> #1>temozolomide, showing that #32 and #20 may be a novel class of putative drugs for the treatment of glioblastoma multiforme by down-regulation of key targets that are critical for GBM survival and metastasis.

Introduction: Myeloid-derived suppressor cells (MDSC) are induced from myeloid-precursor cells by cancer-mediated signals, and play an important role in tumor immune evasion. TGF-β1 is a highly pleiotropic cytokine and is upregulated in the tumor microenvironment and immunosuppressive effects of TGF-β1 on tumor, lymphocytes, and macrophages are well-described, little is known about the direct effects of TGF-β1 on MDSC development. Therefore, the goal of this study was to evaluate the effect of TGF-β1 on the generation and function of MDSC, including its effects on T cell proliferation and tumor growth. Method: MDSC were generated from bone marrow of naive mouse using tumor conditioned medium in the presence (TGFβ-MDSC) or absence of TGFβ-1 (Control-MDSC). They were further enriched for CD11b+ cells and used in MDSC suppression assay and tumor co-culture assay to assess T cell proliferation and tumor death. Flow cytometry was used to characterize CD11b+ and CD11c+ macrophages and MDSC to assess tumor microenvironment (TIME), a lack of tumor-specific T-cell generation, and T-cell exhaustion. As a result, the field of cancer immunotherapy is realizing that strategic combinatorial treatments will be necessary to overcome the challenge posed by established solid tumor cancers. Methods: In this study, using a syngeneic model of HPV-associated head and neck cancer, we developed a combinatorial treatment strategy optimizing localized tumor irradiation, programmed-death receptor-1 (PD-1) immune checkpoint inhibition, and TIME immunomodulation using a previously optimized regimen of cyclophosphamide (CTX) and a selective INO inhibitor (NL1). Results: Preliminary data suggests that this combinatorial strategy promotes synergistic treatment effects, with the full

Treatment/Therapeutics

Moreover, the combinatory treatment increased significantly percentages of dendritic cells (DC) (1.8-fold) and macrophages (2.7-fold) in tumor-draining lymph nodes, compared to CRT alone. These further corroborated these effects as it showed upregulation of gene sets related to function of both cell populations in tumor after combinatory treatment, suggesting that treatment improves T cell activation by favoring antigen presentation. Conclusions: Overall, the enhancements in CD8 T cell specific and activity are well as the additional treatment responses suggests that CTXL-NIL can enhance susceptibility of immune-refractory tumors to CRT by increasing the DC and macrophage function.

292 Poster Session A

TGF-b1- reprogrammed myeloid-derived suppressor cells promote long-term tumor control and lose immunosuppressive function

Radhimi Jayaraman, Baylor College of Medicine; F. Parikh; J. Newton; R. Krupar; R. Parthar; A. Sikora

Introduction: Myeloid-derived suppressor cells (MDSC) are induced from myeloid-precursor cells by cancer-mediated signals, and play an important role in tumor immune evasion. TGF-β1 is a highly pleiotropic cytokine and is upregulated in the tumor microenvironment and immunosuppressive effects of TGF-β1 on tumor, lymphocytes, and macrophages are well-described, little is known about the direct effects of TGF-β1 on MDSC development. Therefore, the goal of this study was to evaluate the effect of TGF-β1 on the generation and function of MDSC, including its effects on T cell proliferation and tumor growth. Method: MDSC were generated from bone marrow of naive mouse using tumor conditioned medium in the presence (TGFβ-MDSC) or absence of TGFβ-1 (Control-MDSC). They were further enriched for CD11b+ cells and used in MDSC suppression assay and tumor co-culture assay to assess T cell proliferation and tumor death. Flow cytometry was used to characterize CD11b+ and CD11c+ macrophages and MDSC to assess tumor microenvironment (TIME), a lack of tumor-specific T-cell generation, and T-cell exhaustion. As a result, the field of cancer immunotherapy is realizing that strategic combinatorial treatments will be necessary to overcome the challenge posed by established solid tumor cancers. Methods: In this study, using a syngeneic model of HPV-associated head and neck cancer, we developed a combinatorial treatment strategy optimizing localized tumor irradiation, programmed-death receptor-1 (PD-1) immune checkpoint inhibition, and TIME immunomodulation using a previously optimized regimen of cyclophosphamide (CTX) and a selective INO inhibitor (NL1). Results: Preliminary data suggests that this combinatorial strategy promotes synergistic treatment effects, with the full
Treatment/Therapeutics

regimen allowing complete rejection of 50% of large established tumors and single treatments promoting only minor delays in tumor growth. Furthermore, these findings establish that the Chk2 inhibitor significantly inhibited tumor growth upon rechallenge indicating the successful generation of tumor-specific immunologic memory. Immune microenvironment analysis using flow cytometry was further used to provide therapeutic mechanistic insight. Within the tumor-draining lymph node radiation alone promoted enhanced T-cell reactivity as it increased at 11 MCF7 T-cell fraction compared to control mice. However, radiation alone also appeared to induce major lymphopenia effects as it promoted a 10-fold depletion in total lymph-node dwelling T-cells with no changes in tumoral T-cell infiltration. Alternatively, CTX/LNIL immunomodulation alone promoted a 50% increase in tumoral T-cell infiltration as expected with the removal of the immunosuppressive TIME; hence, minimal tumor-specific T-cell generation was observed. Finally, when CTX/LNIL and radiation were combined with PD-1 inhibition it reversed radiation T-cell depletion effects and augmented T-cell infiltration. In this study, microarray analysis was utilized to profile the tumor-derived miRs in Vemurafenib-sensitive and resistant melanoma cell lines. Quantitative real-time PCR, Western blot and other molecular techniques were utilized to validate the content of exosomes-associated miRs and their target genes. Results: Our results demonstrated that Vemurafenib-resistant cells exhibit differential expression of miRs and transcripts regarding the Vemurafenib-sensitive cells. Resistant cells had high expression levels of miR-302d and miR-630 compared to parental cells. Various miR-target genes have been identified such as RGS12 and CDC37. These genes were validated on transcript and protein levels. Our ongoing study is designed to determine the potential of exosomal miRs and their target genes for interactions between the factors, the ANOVA results suggest there is a difference in percentage dose deposited for interactions between the factors, the ANOVA results suggest there is a difference in percentage dose deposited between depths. With p > 0.05 when comparing dosimeter types and their interaction at four different depths of 0.5 cm, 1.0 cm, 1.5 cm and 10 cm. The variable of interest is the percentage dose. A two-way ANOVA was used to determine any difference or interaction between the three dosimeter and the four depths. Results: This result of p < 0.05 when comparing at depths suggests there is a difference in percentage dose deposited between depths. With p > 0.05 when comparing dosimeter types and for interactions between the factors, the ANOVA results suggest there is no significant effect between the dosimeter types and their interaction at different depths. Conclusions: The next step is to increase the sample size and to refine procedures to in order to observe and specify factors of interaction.

295 / Poster Session A
Exosomal microRNAs as a novel mechanism of resistance to BRAF-V600E inhibitor in melanoma cells
Sharma Gad, Texas A&M University System Health Science Center; H. Ali; H. Ali; Z. Abd Elmageed

Introduction: Metastasis melanoma associated with BRAFV600E (mBRAF) mutation is the main cause of death in 60–80% of skin cancers. Vemurafenib is an effective gene-targeted therapy for the treatment of mBRAF-associated melanomas. A progression-free survival correlates with mBRAF inhibition, however, a growing challenge emerges as a result of resistance to this drug. Thus, identifying the underlying molecular mechanisms by which resistance to Vemurafenib develops in melanoma patients is urgently needed. Hence, we aim to elucidate the anticipated role of exosomal microRNAs (miRs) and their vesicular cargos in promoting drug resistance in mBRAF-positive melanoma cells. Methods: In this study, microarray analysis was utilized to profile the tumor-derived miRs in Vemurafenib-sensitive and resistant melanoma cell lines. Quantitative real-time PCR, Western blot and other molecular techniques were utilized to validate the content of exosomes-associated miRs and their target genes. Results: Our results demonstrated that Vemurafenib-resistant cells exhibit differential expression of miRs and transcripts regarding the Vemurafenib-sensitive cells. Resistant cells had high expression levels of miR-302d and miR-630 compared to parental cells. Various miR-target genes have been identified such as RGS12 and CDC37. These genes were validated on transcript and protein levels. Our ongoing study is designed to determine the potential of exosomal miRs and their target genes for interactions between the factors, the ANOVA results suggest there is a difference in percentage dose deposited for interactions between the factors, the ANOVA results suggest there is a difference in percentage dose deposited between depths. With p > 0.05 when comparing dosimeter types and their interaction at four different depths of 0.5 cm, 1.0 cm, 1.5 cm and 10 cm. The variable of interest is the percentage dose. A two-way ANOVA was used to determine any difference or interaction between the three dosimeter and the four depths. Results: This result of p < 0.05 when comparing at depths suggests there is a difference in percentage dose deposited between depths. With p > 0.05 when comparing dosimeter types and for interactions between the factors, the ANOVA results suggest there is no significant effect between the dosimeter types and their interaction at different depths. Conclusions: The next step is to increase the sample size and to refine procedures to in order to observe and specify factors of interaction.

296 / Poster Session A
Targeted cancer therapy: Novel Pyrazolobenzimidazole Conjugates as Checkpoint Kinase 2 (Chk2) Inhibitors
Hamed Ali, Texas A&M University System Health Science Center; S. Gailal; B. Standard; S. Khairat; M. Ali; R. El-Shenawy; S. Shourman; Y. Atta; R. Ramdan; H. El Diwani

Introduction: Recently a dramatic development of the cancer drug discovery has been shown in the field of targeted cancer therapy. Checkpoint kinase (Chk2) inhibitors offer a promising approach to enhance the effectiveness of cancer chemotherapy. In this study, many pyrazole-benzimidazole conjugates were designed and twenty one feasible derivatives were selected to be synthesized and subjected to study their antiproliferative effects against Chk2 activity using CycLex Checkpoint Kinase Assay kit-1. The antitumor activity of these compounds was investigated against MCF-7, Hela, and HCT2 cell lines using SRB assay. The potentiating effect of the synthesized Chk2 inhibitors was investigated using genotoxic drugs as cisplatin and doxorubicin on MCF-7 cells. Furthermore, in vivo Chk2 and antitumor activities of 5-nitropyrazole-benzimidazole carbamoylhydrazone (8d) as single-agents and in combination with doxorubicin and cisplatin in breast cancer-bearing animals induced by MNU. In silico study was as single-agents and in combination with doxorubicin and cisplatin in breast cancer-bearing animals induced by MNU. In silico study was designed by docking of the designed and the synthesized compounds into the Chk2 kinase (PDB: 2XBJ) in comparison to the co-crystallized X3L ligand. Results: The revealed potency (IC50) of the studied pyrazole-benzimidazole conjugates ranges from 5.6 to 65.07μM. Interestingly, the activity of cisplatin and doxorubicin were potentiated by the effect of acid derivatives and nitropyrazole-benzimidazole conjugates. Whereas, carbamoylhydrazones and amide pyrazole-benzimidazole conjugates antagonized the cytotoxicity of both genotoxic agents. In the in vivo study exhibited that this combination therapy inhibited the checkpoint kinase activity more than the single treatment. There was a positive correlation between Chk2 inhibition and the improvement in histopathological features. Moreover, the effect of compound 8d alone and in combination with doxorubicin was also studied on cell-cycle phases of MCF-7 cells. Flow cytometry analysis indicated that compound 8d as doxorubicin encouraged S phase arrest whereas, the combination of 8d with doxorubicin induced cell cycle arrest at G2/M in 8% in case of doxorubicin to 51 % for the combination.

420 / CPRIT Grantee Poster Session B
Comparison of a DNA Dosimeter to Conventional Dosimeters for Shallow Depth Radiation Measurements
Brian Quang Bui, The University of Texas Health Science Center at San Antonio; K. McConnell; M. Obeidat; N. Papanikolaou; E. Lopez-Berestein; S. D. Anderson Cancer Center; R. McConnell; A. Naing; G. Lopez-Berestein; S. Fu; A. Tsimberidou; S. Pant; A. Sood

Introduction: Radiation dosimetry plays a large role in cancer therapy by using dosimeters to determine the imparted energy, or dose, to cancer sites. This is important because the energy remaining at a target site is less than when it first originated. Before this decrease occurs, due to the natural attenuation by tissue, a condition called charged-particle equilibrium (CPE) occurs at a specific depth called D-max. Past this point, more accurate measurements can be made. The dose at the shallow depths between the surface of the skin and D-max is difficult to measure with high certainty, and this can be seen by using conventional dosimeters such as films and Optically Stimulated Luminescence Dosimeters (OSLDs) and plotting dose vs. depth to obtain a percentage depth dose (PDD) curve. Typically, this curve is used as a tool to help refine and personalize treatments, so it is very necessary to develop a way to describe dose at shallow depths. During radiotherapy, the fragmentation of double stranded DNA at cancer sites is a direct result from high doses of radiation. With this biological effect, a direct association can be made between the DNA breakages and radiation measurements, as opposed to conventional dosimeters that require correction factors. Methods: In hopes of using this for characterizing shallow depth doses, DNA dosimeters were synthesized via polymerase chain reaction to the Chk2 protein and immobilization and then compared with OSLDs and GAFCHROMIC EBT3 dosimeter film at varying distances from a 6 MV radiation source. To replicate tissue attenuation, phantoms separately containing the DNA dosimeter, OSLD, and film were subjected to constant machine output (2496 Monitor Units (MUs) for the former and 134 MUs for the latter at four different depths of 0.5 cm, 1.0 cm, 1.5 cm and 10 cm. The variable of interest is the percentage dose. A two-way ANOVA was used to determine any difference or interaction between the three dosimeter and the four depths. Results: This result of p < 0.05 when comparing at depths suggests there is a difference in percentage dose deposited between depths. With p > 0.05 when comparing dosimeter types and for interactions between the factors, the ANOVA results suggest there is no significant effect between the dosimeter types and their interaction at different depths. Conclusions: The next step is to increase the sample size and to refine procedures to in order to observe and specify factors of interaction.
tissue), and its important role in promoting tumor growth and metastasis. It has kinase-dependent and independent functions, making it an ideal target for RNAi-based targeting. We have previously reported that EphA2 siRNA incorporated in DOPC nanoliposomes (EPHARNA) was highly effective in reducing EphA2 protein levels after a single dose. In addition, three weeks of treatment with EPHARNA (150 microg/kg twice weekly) in an orthotopic mouse model of ovarian cancer (HeyA8 or SKOV3ip1) significantly reduced tumor growth compared with non-silencing siRNA, and demonstrated synergistic anti-tumor activity when combined with conventional chemotherapy. EPHARNA underwent GLP development in 2 animal models (murine and primate) at M.D. Anderson to support the IND (#72924). The first-in-human trial (NCT01591356) is ongoing and recruiting study subjects. **Methods:** Adult Patients > 18 years of age with histologic proof of advanced recurrent solid tumors, who are not candidates for known regimens or protocol treatments of higher efficacy or priority. All patients (dose escalation and dose expansion phases) must be willing to undergo pre- and post-treatment biopsies. For dose expansion phase, patients must have EphA2 overexpression by IHC evaluation. Enrollment is ongoing for the dose escalation with the plan for dose expansion. **Results:** A total 24 patients have been dosed. Infusion related reactions (fever, chills, hypertension) attributed as DLT’s in the first dosing cohort required amendments to the trial including, an extension in infusion time, post-treatment hydration and steroids. Currently dose level 3 (1012.5 mcg/kg) is enrolled and nearing its safety window assessment. SAE’s were hypertension (n=2), Fever/Chills (N=3), Nausea/Vomiting (N=1). The median number of treatment cycles was 2, range 1 to 6. No objective responses have been observed in the first 2 dosing cohorts, however, 3 patients had confirmed stable disease at 12 weeks. **Conclusions:** Enrollment continues to the dose escalation portion. Dynamic imaging will initiate once the dose level exceeds 1800 mcg/kg.
Spin-value based magnetoresistive nanoparticle detector for applications in biosensing
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Introduction: Magnetoresistive (MR) biosensors have been studied as a possible alternative to fluorochrome and enzymatic biomarker assays. Analog MR sensors are compact, inexpensive to manufacture, highly sensitive, and have shown the potential to detect ~14 10^3 magnetic nanoparticles (MNPs) using high precision electronics. In comparison, the quasi-dimensional MR sensors developed by our team can detect a single 500nm MNP using simple off-the-shelf electronics.

Methods: The sensor is comprised of an optimized spin-valve stack (Ta/Ru/Co/Ru/Co/Co/Ru/Co/Ta) patterned into 700nm X 600nm rectangles. The sensor has two resistance states which depend on the mutual alignment of the magnetization of the two (Co/Ru/Co) trilayers: one trilayer is pinned and the other trilayer switches abruptly at a specific magnetic field. When an MNP is on the sensor, it generates a stray magnetic field that changes the switching field of the sensor. The switching field is measured to determine the presence of bound MNP(s).

Results: A digital voltmeter was used to record the sensor’s resistance while sweeping an external magnetic field between ±400 Oe. The switching field positions of the sensor were -128 Oe and 126 Oe. For proof of concept, 5 µL of a suspension of 500 nm Fe3O4 nanoparticles in DI water at a concentration of 0.1 mg/ml was pipetted on an alumina-coated sensor. With 10 MNPs on the sensor, the switching field positions shifted to -181 Oe and 179 Oe. The switching field returned to its original state after wiping the MNPs off. To demonstrate single MNP detection, an ultra-sharp tungsten tip was used artificially to position a single MNP on the sensor surface. The switching field position is 110 Oe when there was no MNP above the sensor, and changed to 260 Oe when there is a single MNP on the sensor.

Conclusions: The fabricated MR sensor demonstrated the detection of single 500nm MNPs as well as a single 500nm MNP. This method may be effective in the detection of ultra-low concentrations of biomarkers that are expressed only when the disease is present. This aim of the project is the ultrasensitive detection of NK-AR-LK fusion protein that is expressed in anaplastic large cell lymphoma. This is a common tumor in children and young adults. The sensors are inexpensive to manufacture and the reader can be packaged into a low cost portable or mobile system.

The development of a flow-proteometric platform to quantify on-target binding constant and predict treatment drug response
Chao-Kai Chou, The University of Texas M.D. Anderson Cancer Center; P. Huang; H. Lee; Y. Wang; C. Shi; J. Kameoka; M. Hung; P. Tsou

Introduction: The use of flow-proteometric-based single molecule digital platforms to quantify biological complexes and proteins and peptides provides a unique advantage to investigate biological complexes by direct counting. We developed a new method to measure antibody on-target binding constant and complex-biomarker analysis using this technology. Therapeutic antibodies have demonstrated promising success in cancer treatment. However, an antibody with a higher on-target binding efficiency can better suppress the target with less off-target side effects. Thus, we developed a cell-based methodology to directly detect individual antigen-antibody complex after antibody treatment and quantify the on-target dissociation constant (Kd) and off-target ratio. In addition to therapeutic antibody efficacy analysis, complex biomarker measurement can be used to predict cancer drug treatment response. Because signal transduction is delivered primarily via complex formation, the detection of signaling complexes to reveal the signal status is expected to be a better functional biomarker. Since targeted therapy blocks specific cancer signaling pathways, the quantification and identification of complexes can be used to predict the drug treatment response prior to administering the drug(s) to patients. In summary, the new technology we have developed will enable direct quantification of protein complexes with many potential applications in both drug and biomarker development.

Methods: To measure the antibody Kd, we counted the target protein bound to therapeutic antibody in cancer cells. Cetuximab, an anti-EGFR therapeutic monoclonal antibody, was used as a model. EGFR-GFP was expressed in EGFR-nut CHO cells, which were then treated with fluorescence-labeled cetuximab at different concentrations. Cells were lysed and subjected to flow-proteometric analysis to count the amount of antibody, EGFR proteins, and antibody-EGFR complexes. The antibody on-target binding affinity and off-target binding ratio was determined based on the amount of interaction. For complex biomarker analysis, lung cancer cells were treated with and without tyrosine kinase inhibitor (TKI) gefitinib for two hours and the EGFR complex biomarker quantified to determine its sensitivity to gefitinib.

Results: 1) The on-target-Kd of cetuximab in CHO cells with EGFR-GFP expression was 2.3 nM with an off-target ratio of about 30%. 2) Several EGFR complexes including EGFR-JAK1 and EGFR-Met, were demonstrated for their potential to be used as complex biomarker to predict TKI response. Conclusions: We have developed a unique single-molecule detection platform that can evaluate the therapeutic antibody binding efficiency in cells and also monitor the quantity of complex biomarker to predict targeted therapy response that can be applied to both drug development and personalized cancer therapy.

Single molecule protein sequencing
Jagannath Swaminathan, The University of Texas at Austin; A. Bardo; E. Marcotte

Introduction: The paucity of protein biomarkers in cancer diagnosis can be ascribed to the current technical limitations in discovering the changes occurring in the sequences, abundances and modifications in the ~20,000 proteins that occur in human cells. While a variety of technologies have been applied to this problem, including mass spectrometry and antibody arrays, they generally lack the sensitivity and digital quantitation necessary for the complete characterization of the proteome.

Methods: Adapting principles of next generation DNA sequencing technologies, we developed fluorosequencing: a single molecule method for sequencing and identifying proteins in a highly parallel fashion. First, we selectively label peptides at one or more amino acid residues (e.g. lysines) with fluorophores. Millions of individually fluorescently labeled peptides are covalently immobilized on a glass surface. The fluorescence intensity of individual labeled peptides is sequentially removed through Edman degradation, providing positional information for the labeled amino acid residues within each peptide (e.g. x-K-x-x-K). The resulting fluorescence can then be mapped to a reference proteome to identify the originating protein.

Results: We present the theoretical foundation and experimental implementation of fluorosequencing, confirming its utility and sensitivity. With the help of Monte Carlo computer simulations, we quantitatively characterize the most significant experimental errors. Conclusions: We discuss fluorosequencing’s potential for identifying and discriminating proteins along with their diverse modification states arising in cancerous cells.

A Frequency Agile Mixing Front End for Multi-Channel, Multi-Nuclear Spectroscopy
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Introduction: In order to better understand the behavior and treatment of cancer, it is imperative to understand the growth and metabolism of tumors. There are a number of analytical techniques available to this end, but few of them are well suited to the collection of in vivo data. In vitro NMR is a proven tool for studying cancers in vitro, but most of the work done so far has been limited to H. This stems from the fact that most MRI systems have 16-64 1H receive channels, but only have a 1-4 receive channels for other nuclei.

Methods: In order to increase the sensitivity to nuclei other than H, it is advantageous to have a large number of receiver channels that are capable of receiving a broad range of nuclei. Using multiple receive channels increases the sensitivity of the NMR experiment. This is almost essential for in vivo study of natural such as 13C, which have very poor natural sensitivity. This work shows that radiofrequency mixers can be used to adapt a system’s proton array receiver for use with other nuclei, such as 13C or 31P. RF mixers are used to convert the frequency of the received signal from the frequency of the other nucleus to the H frequency. By using non-magnetic active mixers, the hardware required to perform this conversion can be located in the scan room or even in the bore of the MRI magnet. A frequency translation system has been developed to convert 16 channels of other nuclei to H. This system allows an MRI system’s existing H receivers to be adapted for use with other nuclei without any decrease in SNR. The system is flexible with regards to MRI field strength and nuclei. Data have been acquired at 4T and 7T from 13C, and H. Additionally, the system is tolerant of H decoupling, which can be used to further increase the sensitivity of C spectroscopy.

Conclusions: A frequency translation system has been developed to improve the sensitivity of in vivo 13C and other non-H nuclei. This system allows existing multichannel MRI receivers to be adapted to receive other nuclei, greatly improving the sensitivity of these nuclei. In vivo measurement of 13C NMR spectra will increase our understanding of tumor metabolism and help us to monitor the effectiveness of treatment regimes.
ABSTRACTS

Product development research and analysis provides a means to improve the efficiency of clinical trial management. Structured reporting combined with automated tumor measurements may provide an alternative to FIT and other stool-based tests for early cancer detection.

Methods: We evaluated a blood-based marker panel including galectin-3 ligand, MAPRE1, galectin-3, CEA, CYFRA21, ferritin, CRP16 dependent sensing mechanism of J-aggregate breakdown, resulting in a strong absorbance at ~890 nm where low blood absorbance and tissue scattering results in strong PA signal penetration depth sufficient for whole mouse imaging; (ii) strong PA signal enhancement; and (iii) the capability of enabling simple image processing algorithms for quantitative PA imaging. Targeting and viability for at least 80% of the 3D analysis and a radiologist’s verbal descriptions of the image findings and results, tags the images with metadata using natural language processing referenced for SNOMED-CT terms coded by the CPT, ICD-10-CM) relationship between terms, such as SNOMED-CT and ICD-10-CM) to describe anatomical locations and diagnostic detail, and assembles a multimedia structured report with related information displayed in graphical timelines. In addition, the system integrates treatment information coded by the OPT, ICD-10-PCS, and RoNorm ontologies. Information at the beginning of a timeline often represents presenting signs/symptoms of disease, whereas the information at the end of a timeline indicates an outcome based on pathological or clinical findings. The graphical representation of information, including tumor metrics, enables the calculation of disease response criteria (e.g., RECIST, irRECIST). For cohorts of subjects enrolled in clinical trials, data mining tools incorporating the ontological structures have been developed to enable the calculation of population statistics and answer queries such as, what percentage of patients with disease X treated with regimen Y have responded to therapy? Results: A solution for creating medical knowledge and organizing outcomes is needed to provide a comprehensive and effective approach to managing medical knowledge in health care settings. The system is currently in beta testing at our institution and has been used to report on the outcomes of 300 subjects enrolled in clinical trials. Conclusions: Multimedia structured reporting provides a means to connect interrelated disease and treatment information in graphical timelines from which healthcare outcomes and medical knowledge can be generated. This novel reporting system could form the basis for the next generation of electronic medical records.
in a 100 nm wavelength blue-shift and an emergence of strong near-infrared fluorescence. **Conclusions:** PARace shows high photostability, signal enhancement, and targeting capabilities, both in vitro and in vivo. Likewise, the sensing capabilities enabled by the spectral shift and increased fluorescence upon receptor-mediated cellular uptake provides non-invasive photoacoustic (PA) imaging system capable of simultaneous anatomical, functional, cellular and molecular visualizations of complex biological cells. By developing the technology, we hope to enable PA imaging to significantly improve preclinical cancer research, expediting the development of new drugs, treatments, and diagnosis platforms.

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**Poster Session B**

**High-flow rate system for rapid isolation CTCs from blood**

*Andrew Ellington, The University of Texas at Austin*

**Introduction:** A key to frequent monitoring of cancer patients’ response to therapy as well as characterization of oncogenesis is the ability to isolate circulating tumor cells. Unfortunately, these cells are present in vanishingly rare amounts in blood and therefore cannot be found by pin prick blood tests. Traditional cell sorting methods like flow cytometry require relatively large numbers of cells to be present. Other microfluidic devices either operate very slowly, or lack sensitivity and specificity, thereby delaying the possibilities for diagnosis or prognosis. We present a rapid, robust, and highly sensitive and selective method for the isolation of individual tumor cells from standard blood samples, and show how this method is enabling new cancer diagnostics and therapeutics. **Methods:** The basis of the method is a simple but novel patented device that utilizes a unique combination of magnetic capture and flow to directly isolate CTCs from blood. Magnetic beads bearing antibodies against one or more tumor antigens filter to particular cells, which are then in turn captured from a flowstream onto a porous surface. While the magnetic beads themselves can fit through the pores, cells bearing the magnetic beads are too large and are captured in individual pores, and residual cells that are non-specifically captured on the surface can be washed away. Upon removing the magnet, the cells can then be conveniently collected. **Results:** The system achieves capturing of extremely rare cells with 90% or better sensitivity, while discarding more than 99.99% of unwanted blood cells with remarkable speed (2 mL/min of flow rate) and simplicity. The system has so far been tested on 100s of patients of the Indiana University Simon Cancer Center as has been shown to successfully capture CTCs of non-small and small cell lung cancer, pancreatic cancer, breast cancer, bladder cancer and prostate cancer. The system is currently being used to assess how triple negative breast cancer patients with post-surgery residual disease respond to genotypically directed therapy. **Conclusions:** The versatility of the system to practically capture any cell that manifests a surface antigen renders it extremely useful for numerous applications. A study in collaboration with the UT Dell Medical School for capture and genetic analysis of fetal cells in maternal blood is underway. The 8 issued as well as pending patents related to the technology has been licensed for commercialization.

**Poster Session B**

**High-flow rate system for rapid isolation CTCs from blood**

*Kevin McBride, The University of Texas M.D. Anderson Cancer Center; M. Zelazowska; J. Plummer; Y. Mu; A. Guilmette*

**Introduction:** Plasma cells (PC) are terminally differentiated antibody secreting cells that are the major source of serum immunoglobulins (Ig). Identifying antigen specific PCs is an important goal for both immunologic studies and monoclonal antibody production. However, the lack of Ig surface expression has impeded direct identification of PCs expressing antigen specific antibodies. **Methods:** We devised a novel method we termed antigen specificity of plasma cell determination (ASPCeD), to isolate live PCs producing antigen specific antibodies from total spleen or bone marrow populations using one-step flow cytometry. Using ASPCeD and existing single cell immunoglobulin amplification and cloning techniques we rapidly produced recombinant antibodies to desired targets. This allows rapid production of sequence defined antibodies on a cost basis lower than existing methods. **Results:** To demonstrate the utility of this technique we immunized mice against several protein, peptides and antibodies with post-translational modifications as immunogens, and combined ASPCeD with established single cell immunoglobulin cloning. We rapidly produced sequence diverse, recombinant monoclonal antibodies, highly specific for the targets. Furthermore, we have produced post-translational modification specific antibodies using this technique which include sering phospho-specific and arginine methylation specific antibodies. Other targets include viral proteins and cellular proteins. **Conclusions:** We rapidly produced sequence defined antibodies. The cost basis was lower than existing methods. As a demonstration were able to produce multiple antibodies specific to a desired target in 35 days. Thus, ASPCeD is a novel method to identify antigen specific PCs and an improved means for recombinant antibody production.
CT-179 selectively targets Olig2-positive glioblastoma stem cells and demonstrates potent anti-tumor activity in glioblastoma (Gordon Alton, Curtana Pharmaceuticals, Inc.; G. Beaton; S. Knowles; S. Kesan; G. Stein)

Introduction: Olig2 is a lineage-specific bHLH transcription factor in normal brain development and has been shown to be a critical oncogene controlling the tumorigenesis, growth, invasion, differentiation and radiation resistance of glioblastoma (GBM). Importantly, Olig2-positive glioma stem-like cells (GSCs) are responsible for the recurrence of disease that occurs in most of the GBM patients. CT-179 is a small molecule (397 kD) that was designed to bind to the dimerization interface of Olig2. Methods: Internal research Results: Based on comparison to shOlig2 effects in GSCs, the mechanism of action of CT-179 is through modulation of the transcription of Olig2-targeted genes. CT-179 inhibits cellular growth and induces apoptosis of Olig2-expressing GSCs at low nanomolar concentrations (average GS50=154 nM; n=18). CT-179 also causes mitotic catastrophe and a corresponding G2/M arrest of GSCs. The compound is completely water soluble, is nearly 100% orally bioavailable, demonstrates a long duration of pharmacologic action suitable for once daily dosing, and readily crosses the blood-brain barrier. As such, it achieves therapeutically effective concentrations in the brain. Immunohistochemistry demonstrates a reduction of Olig2-positive cells in tumors bearing animals. CT-179 significantly extends survival of mice implanted orthotopically with patient-derived GSCs. Importantly, CT-179 combined with standard of care temozolomide and radiation dramatically inhibits tumor growth compared to either treatment alone. Conclusions: CT-179 represents a novel agent which selectively targets GSCs with great potential as an adjunctive therapy in the treatment of GBM and other gliomas.

309

Stabilization of b-catenin as a potential therapeutic target for desmoid tumors

Poster Session B

Davide Brengos; Beta Cat Pharmaceuticals LLC; D. Kohler; F. Jin; A. Zewdu; K. Batte; G. Lopez; R. Soldi; S. Horrigan; L. Casadei; M. Welliver; A. Strohecker; R. Pollack; D. Lev

Introduction: Desmoid tumors (DTs) are rare mesenchymal lesions that can recur repeatedly. When feasible, DTs are surgically resected; however, this often results in high recurrence rates. While many therapeutic options are available, the standard treatment for desmoids remains uncertain and the overall response to most treatment options remains modest, suggesting a clear ongoing need for better and more individualized approaches. Most DTs commonly feature deregulation of the Wnt pathway. For that reason, the inhibition of Wnt/b-catenin signaling emerges as a potential therapeutic target for these tumors. Methods: A panel of DT cell lines was exposed to increasing concentrations of BC2059 in vitro and evaluated for cell proliferation and colony formation capacity. Antitumor effects were assessed in vivo by cell cycle, apoptosis, and migration analysis by various endpoint evaluations with both tumor-bearing mice and tissue harvested from xenograft studies. Cells were analyzed for the association of b-catenin with TBL1 by immuno precipitation (IP) analysis. To further understand the effects of BC2059 treatment on DTs we analyzed the expression of b-catenin pathway components in DT cell strains treated with BC2059 using real-time PCR and western blotting. Results: BC2059 markedly inhibited proliferation, capacity of colony formation, migration and invasion of mutated DT cells. In wild-type cells (cell strains lacking detectable b-catenin mutation), BC2059 had no effect on colony formation, migration, and invasion and required a much longer time to inhibit cell proliferation. Comparison of b-catenin mutation between the original tumor and the associated cell strain was the primary method used to differentiate desmoid tumor cells from fibroblasts. Therefore, cell strains lacking detectable b-catenin mutation (a rare condition with limited clinical presentation) could be comprised of primarily fibroblast cells and not tumor cells. This is one possible explanation for the lack of effect of BC2059 on cell strains associated with tumors in cell strains mutated DT cells caused by BC2059 was due to apoptosis. Treatment with BC2059 led to a reduction of b-catenin associated TBL1 in all mutated DT cells, resulting in a reduction of nuclear b-catenin. Consequently, levels of genes that are targets of b-catenin (e.g MDK, AXIN2) were found to be downregulated after BC2059 treatment. Conclusions: Our findings suggest that BC2059 has significant antitumor activity against b-catenin mutated DTs through stabilization of b-catenin that leads to downregulation of its target genes. Thus, BC2059 may comprise an alternative strategy for the treatment of desmoid tumor patients.

310

Investigational new drug (IND)-enabling studies for Sepin-1, a novel Separase inhibitor for triple negative breast cancer (TNBC) therapy

Poster Session B

Nenggang Zhang, Baylor College of Medicine; A. Sarkar; D. Pali

Introduction: Separase is a chromosomal cohesion-resolving enzyme. It is overexpressed in multiple human tumors including TNBC. Separase is an oncogene and its overexpression causes mammary tumorigenesis in mouse models. To modulate the activity of Separase, we identified a small molecular inhibitor called Separase inhibitor 1 (Sepin-1) that inhibits separase activity in a non-competitive way. Sepin-1 inhibits the growth of breast tumor cells in vitro and in vivo. To develop Sepin-1 for preclinical and clinical trial, we performed preclinical studies on xenograft survival and pharmacokinetics (TK) studies to assess its toxicity in animals. Methods: Sepin-1 was administered intravenously (IV) to Sprague-Dawley rats and Beagle dogs to determine the maximum tolerated dose (MTD) of Sepin-1 with a single IV injection and potential toxicity and TK profile, once daily for 4 consecutive days. On Days 1 and 7, blood samples at various time points were collected from animals for TK evaluation. Results: A single IV injection of Sepin-1 to rats was toxic at 75 mg/kg. When the dose level was reduced to 40 and 60 mg/kg for males and females, respectively, except for minimal transient clinical signs of urine discoloration and/or hypoactivity, no abnormalities were observed. In 7-day toxicity study, except one female rat death at 50 mg/kg toxicity group during dosing on Day 3, there was no remarkable signs of toxicity observed in animals dosed with vehicle control and/or Sepin-1 at 5 and 20 mg/kg doses. When Sepin-1 was dosed with a single IV injection in Beagle dogs, there was no treatment-related severe toxicological events at 10, 15 and 20 mg/kg, but there were multiple clinical signs of toxicity at 25 mg/kg. When 5 mg/kg or 15 mg/kg of Sepin-1 was administered IV once daily over a period of 7 days, there was no remarkable and/or non-severe treatment-related findings. TK analysis indicated that Sepin-1 has a long half-life of 6.6 - 10.7 h, a high volume of distribution and high clearance in dogs. Conclusions: Based on the observation that there are no remarkable clinical findings, body weight changes and macroscopic findings in animals, the MTD of Sepin-1 administered intravenously once daily in Sprague Dawley rats and Beagle dogs are 10 and 15 mg/kg, respectively, and the MTD of Sepin-1 administered once daily for seven consecutive days in rats and dogs are 20 mg/kg and 15 mg/kg, respectively. In both dogs and rats, Sepin-1 has a long half-life and high volume of distribution and clearance.
ABSTRACTS
PRODUCT DEVELOPMENT

312  CRPT Grantee Poster Session B
Depleting blood arginine with AEB1102 (Pegylarginase) exerts additive anti-tumor and synergistic survival benefits when combined with anti-PD-L1 Giulia Agnello, Aglea BioTherapeutics; M. Badeaux; S. Alters; D. Lowe; S. Rowlinson

Introduction: Tumor dependence on specific amino acids for survival and proliferation is well recognized and has been exploited effectively in the clinic through the use of asparaginase for the treatment of acute lymphoblastic leukemia. Sensitivity of tumors to L-Arg deprivation results from an impaired ability to synthesize L-Arg, most commonly due to decreased functional expression of argininosuccinate synthase. Native human arginase 1 is not a viable drug candidate due to low bioavailability and instability (H2N-DN6) has developed a novel cobalt-substituted, PECoated human arginase 1 (AEB1102, Pegzlararginase) with enhanced pharmacological properties. We and others have successfully utilized arginase 1 to impair an anti-tumor effect through L-Arg starvation in multiple tumor types in vitro and in vivo (e.g. AEB1102 single agent efficacy in neuroblastoma, SCLC, sarcoma, large cell NSCLC, Myelogenous leukemia). Given that arginase 1 has been reported to be immune suppressive, immune neutral (PMID: 23717444), or immune promoting (PMID: 27043409) in different experimental settings and by different groups, we have investigated the impact of systemic depletion of L-Arg on the anti-tumor efficacy of immune checkpoint inhibitors (mAbs). Murine syngeneic models (e.g. CT26, MC38) were dosed with AEB1102 alone and in combination with immunomodulatory anti-PD-L1 monoclonal antibody (mAb). Results: Combination therapy of AEB1102 with anti-PD-L1 resulted in an additive anti-tumor effect with improved survival benefit (median survival in vivo for murine Lewis lung (LL55-120%) compared to AEB1102 (ILS 29-33%) and anti-PD-L1 (ILS 7-33%) monotherapies. In addition, in the CT26 model, complete tumor regression (non-palpable tumors) was observed in 37% of the mice; importantly, complete responses were observed only in the combination therapy group. When the complete responders were re-challenged with fresh CT26, tumor failure to establish suggests the development of an immune memory response as a result of the previously administered combination therapy of AEB1102 and anti-PD-L1. Administration of AEB1102 as a monotherapy or in combination with anti-PD-L1 in the CT26 model was associated with an increase in tumor infiltrated CD45+ cells, indicating that AEB1102 promotes T-cell accumulation in the tumor microenvironment. Conclusions: Collectively, these results demonstrate that in addition to tumor growth inhibition, L-Arg depletion in the tumor microenvironment enhances the effectiveness of immune checkpoint blocking antibodies.

313  CRPT Grantee Poster Session B
NKT cells expressing a GD2-specific chimeric antigen receptor with CD28 endodomain and IL-15 undergo dramatic in vivo expansion and mediate long-term antitumor activity in a xenograft model. Leonid Metelitsa, Baylor College of Medicine; W. Huang; D. Liu; M. Wood; L. Guo; G. Dotti

Introduction: Via24-invariant Natural Killer T cells (NKTs) preferentially localize to sites of inflammation and other types of tumors. NKTs have natural antitumor properties that make them attractive as a carrier of tumor-specific chimeric antigen receptors (CARs). We previously demonstrated that adoptively transferred NKTs expressing GD2-specific CARs (CAR-GD2) can effectively localize to the tumor site and mediate antitumor activity in a xenograft model of neuroblastoma in NSG mice. In this study, we explored whether expression of IL-15, the common cytokine receptor gamma chain (CGR), and functional properties of these receptors will inform the development of mAb therapeutics.

Results: NKT cells expressing a GD2-specific CAR GD2 construct, encoding either CD28 or 41BB costimulatory endodomain and IL-15 in the CAR design enables potent in vivo expansion and antitumor activity of CAR-GD2 NKTs that should be considered for immunotherapy of neuroblastoma and other solid tumors.

314  CRPT Grantee Poster Session B
Phase 1b randomized, multi-center study of oncolytic adenovirus DNX-2401 for recurrent glioblastoma shows improved survival compared to historical controls. Bret Ewald, DNAtrix, Inc.

Introduction: DNX-2401 is a conditionally replicative oncolytic adenovirus with enhanced, tumor-specific infectivity that elicits tumor cell killing and antitumor immunity, leading to a long-lasting therapeutic effect. DNX-2401 has been granted Fast Track designation by the FDA and PRIME designation by the EMA for high grade glioma. A product development grant from the Cancer Prevention and Research Institute of Texas (CPRIT) supports the manufacturing and clinical testing of DNX-2401. Methods: A multi-center, Phase 1b study of DNX-2401 with or without interferon gamma (IFN-2401) conducted to evaluate safety and antitumor activity in patients with recurrent glioblastoma. Thirty-six patients with biopsy-confirmed glioblastoma at first or second recurrence received a single intratumoral injection of DNX-2401 and were randomized to receive subcutaneous interferon (Actimmune, 50 mcg/m^2) three times per week starting at 7 days after DNX-2401 injection and were randomized to receive subcutaneous interferon (Actimmune, 50 mcg/m^2) three times per week starting at 7 days after DNX-2401 injection (17/36) or to be followed without further treatment (9/36) for safety and survival. Ten additional patients (10/36) received an intratumoral DNX-2401 injection via a specialized cannula (Alcyone MEMS cannula) to test delivery efficiency. Results: In the ten patients in which DNX-2401 was administered via the Alcyone cannula, semi-quantitative analyses indicated successful DNX-2401 infusions in all cases, without evidence of backflow. The most frequent DNX-2401-related adverse events were grade 1/2 headache, fatigue, muscular weakness, nausea, and somnolence. Prolonged survival was achieved for patients treated with DNX-2401 alone (range 10-36 months) compared with patients treated with anti-PD-L1. Conclusions: DNX-2401 was well tolerated and showed clinical activity after a single injection when administered with or without interferon gamma. DNX-2401 administration using a specialized cannula provides a standardized method of intratumoral administration. The clinical benefit provided by DNX-2401 supports continued development of DNX-2401 for recurrent glioblastoma.

315  CRPT Grantee Poster Session B
A humanized antibody blocks LILR4B receptor-ligand interaction with potent therapeutic efficacy for acute myeloid leukemia. Xuanyun Gui, The University of Texas Health Science Center at Houston; M. Deng; N. Zhang; A. Zhang; Z. An

Introduction: Leukocyte Immunoglobulin-Like Receptor B4 (LILR4B) is highly expressed on acute myeloid leukemia (AML) cells, suppresses T cell activation and supports AML cell infiltration through its downstream signaling. In contrast to other molecules used as therapeutic targets, which are expressed on a wide range of normal immune cells, LILR4B expression is restricted to monocytic AML cells. Thus, LILR4B is a strong candidate target for novel monoclonal antibody (mAb) based therapeutics which are urgently needed for AML treatment. Previously developed immune checkpoint therapeutic antibodies only boost immune activation, but have no effect on tumor cells. Ideally, therapeutics could be developed with multiple mechanisms of action against AML. Better understanding of the interactions of receptors on AML cells and antibodies targeting these receptors will inform the development of mAb therapeutics.

Methods: Mouse LILR4B antibodies were produced in Acholeplasma laidlawii by transient transfection. Infusion of single memory B cells from a rabbit immunized with the LILR4B extracellular domain (ECD) antigen and screened against a battery of in vitro binding and functional assays. One of the functional assays used a stable chimeric receptor reporter cell system which tests the antibody’s ability in blocking ligand-receptor interactions. Three concordant anti-leukemia activities were demonstrated in vitro and in vivo for the lead antibody: 1) stimulation of T cell activation, 2) inhibition of monocytic AML cell infiltration, and 3) antibody-dependent phagocytosis (ADCP).

Conclusions: A panel of LILR4B targeting antibodies was generated and characterized. The antibodies potently inhibit AML cell growth and migration by specifically...
318 CPRIT Grantee Poster Session B

A novel LSD1 inhibitor Seclidemstat as a promising candidate for the treatment of prostate cancer

**Introduction:** Lysine-specific demethylase 1 (LSD1) overexpression correlates with disease progression and castration resistance in prostate cancer. LSD1 is a coregulator of ligand-independent androgen receptor signaling and has been examined for the cancer therapeutic efficacy in combination with Seclidemstat (SP-2577), a novel small molecule reversible inhibitor of LSD1 in several models of advanced-stage prostate cancer with various status of androgen receptor (AR) expression. **Methods:** A panel of prostate cancer cell lines with various AR status -DU145, LNCaP (AR-), LNCaP-AR (AR-), LNCaP-AR (AR-FL), 22Rv1 and VCaP (AR-FL and AR-SV7) - and the normal prostate epithelial cell line RWPE-1, were used to examine the cell survival, colony formation, histone methylation, LSD1 expression, LSD1 and AR interaction upon treatment with Seclidemstat. Single-agent in vivo efficacy was examined in 22Rv1 xenograft in nude mice in comparison with docetaxel. In vitro combination studies, using Seclidemstat with docetaxel or enzalutamide, were performed to assess the synergy. (AR-FL: full-length androgen receptor; AR-SV7: androgen receptor splice variant 7) **Results:** Seclidemstat potently inhibits the growth of all 5 prostate cancer cell lines tested regardless of AR status, while has no effect in the proliferation of RWPE-1 control cells. Seclidemstat also inhibits the colony formation of DU145, 22Rv1 and LNCaP cells. Seclidemstat treatment causes a dose-dependent increase in H3K9me2 (histone H3 lysine 9) levels and a decrease in LSD1 expression in both LNCaP and PC3 cells. Seclidemstat also caused a decrease in the LSD1-AR interaction in LNCaP cells. Orally-administered Seclidemstat significantly reduced the tumor growth of 22Rv1 xenografts in mice comparable to that of docetaxel with no apparent toxicity. Seclidemstat potentiated the anti-proliferative effect of enzalutamide in AR+ prostate cancer cell lines, whereas Seclidemstat in combination with AR inhibitors shows promising activity in vitro in both androgen-dependent and independent cell lines and inhibits tumor growth of castration-resistant 22Rv1 xenograft in vivo. Seclidemstat also shows promise in combination therapy with standard of care enzalutamide and docetaxel.

**Conclusion:** These studies indicate that Seclidemstat is a promising candidate for the treatment of prostate cancer.

319 CPRIT Grantee Poster Session B

Phase I trial evaluating genetically modified autologous T cells expressing a T-cell receptor recognizing a cancer/germline antigen in patients with squamous NSCLC or HNSCC

**Introduction:** Immuno therapy has dramatically changed the landscape of therapeutic options in oncology. Adoptive cellular therapy is one of the major drivers of this success, which includes the administration of autologous or allogeneic anti-tumor T lymphocytes after ex vivo manipulation and expansion. IMA201-101 is a first-in-human trial testing IMA201 product in patients with recurrent or refractory advanced squamous non-small cell lung cancer (NSCLC) or head and neck squamous cell cancer (HNSCC), whose tumors express the targeted antigen. IMA201-101 is an open-label dose-escalating phase 1 trial investigating safety, tolerability, and signs of biological and clinical activity in end-stage cancer patients. The IMA201 product are T cells engineered to express a naturally occurring (non-affinity matured) T-cell receptor (TCR) specific to a cancer-germline peptide bound to HLA-A*02:01. The target peptide has been characterized in depth by Immatics' proprietary antigen discovery technology, XPARIDENT®. The XPARIDENT® platform applied two independent methodologies to confirm tumor selectivity of the target versus various healthy tissues: i) quantitative immunopeptidome analyses by mass spectrometry and ii) quantitative mRNA expression analyses by RNASeq. The TCR used for IMA201 shows an exceptional specificity profile. TCR-engineered T cells showed specific recognition of tumor cell lines and lack of recognition of healthy normal cells. **Methods:** Only HLA-A*02:01 positive patients expressing the specific target above a pre-defined threshold as determined from a tumor biopsies are eligible for the intended IMA201-101 clinical trial. If a patient meet the leukapheresis criteria, a leukapheresis is performed to manufacture the autologous, TCR-engineered IMA201 T-cell product. The ACTengine® T-cell manufacturing process uses cyropreserved peripheral blood mononuclear cells isolated from a patient’s leukapheresis samples. After activation, the cells are transduced with a lentiviral vector encoding the specific TCR, then expanded before harvest and cryopreservation. The ex vivo expanded IMA201 T-cell product is infused into the pre-
conditioned (lymphodepleted) patient. Patients participate then in an extensive post-infusion biomarker program investigating i) the persistence and stability of IMA201 T-cells in vivo and ii) the capacity of IMA201 T-cells for clinical success, and iii) target expression levels in the tumor before and after the T-cell infusion. Results: Overall, the goal of the ACTengine® IMA201-101 is to determine if IMA201 T-cell treatment can safely and effectively manage the tumors of target positive patients with recurrent or relapsed advanced squamous NSCLC and HNSCC.

320 CPRIT Grantee Poster Session B
Phase I adoptive cellular therapy trial with autologous, multi-target CD8+ T-cells in patients with relapsed and/or refractory solid cancers (ACTolog®. Steffen Walter, Immunetics Biotechnologies; S. Kuttuff; C. Stewart; A. Mohamed; Y. Bulliard; O. Schoor; A. Satelli; N. Hilf; K. Sieger; J. Fritsche; D. Maurer; C. Reinhardt; H. Ma; T. Weinschenk; H. Singh; C. Yee; A. Tsimberidou; P. Hwu
Introduction: Immunotherapy has dramatically changed the landscape of therapeutic options in oncology. Adoptive cellular therapy (ACT), which includes the administration of autologous or allogenic anti-tumor T lymphocytes after ex vivo manipulation and expansion, is one of the major drivers of this success. To date, only a relatively small proportion of patients has benefited from these advances due to i) heterogeneity of tumor antigen expression in cancer patients, ii) observance of significant side effects in ACT patients due to the release of targets or ii) tumor escape (e.g. only one target is addressed). The IMA101 (ACTolog®) concept, utilizing antigen specific T cells, is intended to address these limitations by introducing multiple novel tumor targets, identified by the Immunetics proprietary XPRESSION® technology, as the multi-target approach. ACTolog® is a personalized approach where autologous T-cell products are manufactured against the most relevant tumor target peptides (from a predefined target warehouse) for an individual patient whose tumor is positive for at least one target. Methods: IMA101-101 is a first-in-human clinical trial in patients with relapsed or refractory solid cancers including but not limited to ovarian, esophageal, gastric and NSCLC whose tumors express at least one (and up to 4) target(s) from a predefined warehouse of 8 cancer targets. Patients will be included depending on their HLA type and the expression of warehouse target(s). As the patients participating in this trial are expected to have a high unmet medical need (e.g. very poor prognosis and/or refractory or recurrent disease following multiple lines of established therapy), treatment with IMA101 T-cell products will take place when patients experience recurrence or progressive disease or if therapy is no longer warranted. Patients receive their last line of established therapy during the production phase of the IMA101. Results: The primary goal of the trial is to assess the safety profile of the underlying concept of autologous T-cell therapy on the basis of targets identified by the XPRESSION® platform. Conclusions: The ACTolog® concept accounts for: 1) the individuality of each tumor as may be introduced by ex vivo manipulation, 2) the heterogeneity, as a multi-target approach intended to generate broad anti-tumor activity that is more likely to be effective and that prevents tumor escape or evasion, and 3) the scarcity of suitable tumor antigens for ACT by using novel tumor targets identified by XPRESSION®.

321 CPRIT Grantee Poster Session B
Optimization of reconstituted High Density Lipoprotein nanoparticles for short-interfering RNA Delivery Linda Mooberry, University of North Texas Health Science Center at Fort Worth; N. Sabnis; S. Raut; A. Lacko
Introduction: The objective of these studies was to characterize short-interfering RNA transporting HDL nanoparticles (rHDL/siRNA NPs) and to evaluate their suitability for translation toward clinical applications. Previous studies have shown that rHDL NPs are capable of promoting the delivery and retention of short-interfering RNA (siRNA) by cancer cells and tumors (Shahzad et al., 2011). Methods: To formulate rHDL/siRNA, cholate dialysis, a chemical dispersion process or through the NanoAssembler™ microfluidics instrument (Precision NanoSystems Vancouver Canada). Characterization of rHDL NPs was carried out using dynamic light scattering (DLS), compositional analysis, transmission electron microscopy, and agarose gel electrophoresis. Efficacy of the rHDL NPs was evaluated through transfection studies utilizing confocal microscopy and Western blotting. Results: The size of the rHDL/siRNA complexes by DLS was found to be 68.2 ± 3.0 nm for nanoparticles prepared by cholate dialysis and 35.9 ± 2.9 nm for nanoparticles prepared by microfluidics. However, transmission electron microscopy showed smaller uniform spherical nanoparticles with a diameter of 23.9 nm ± 2.9. The siRNA was encapsulated in a complex as shown by a mobility shift assay with agarose gel electrophoresis. The formulation showed good stability after lyophilization and reconstitution with minimal change in size or loss of RNA content. Knockdown of the target transcription factor STAT-3 was observed in the SKOV-3 ovarian cancer cell line. Evidence for a SR-B1 receptor-mediated uptake mechanism, and a high payload uptake, was blocked by an anti-SR-B1 antibody. Conclusions: The optimized rHDL/siRNA formulation has a small diameter, good siRNA incorporation efficiency that is biologically active. Importantly for potential clinical applications, this formulation was found to be stable after lyophilization. This study demonstrates the first formulation of NPs with a protein component, using the NanoAssembler instrument.

322 CPRIT Grantee Poster Session B
Clinical safety and efficacy of MDNA55: results of 3 studies in recurrent malignant gliomas Martin Byxov, Medicenna Therapeutics, Inc.; R. Abi-Habib; R. Merchant; F. Merchant
Introduction: MDNA55 is a targeted immunotherapeutic agent comprising a circularly permuted interleukin-4 (cpl4) fused to a truncated version of Pseudomonas exotoxin A (PE). MDNA55 binds to the interleukin-4 receptor (IL-4R), over-expressed by glioblastoma cells and by non-malignant cells of the tumor microenvironment (TME) such as myeloid-derived suppressor cells (MDSCs). Methods: Three clinical trials of MDNA55 (two Phase I and one Phase II) were carried out in patients with recurrent malignant gliomas. Most patients received a single dose of MDNA55 by direct intra-tumoral infusion over a period of 3 to 5 days. Three studies received up to three doses. Results: A total of 72 patients treated with intratumoral doses of MDNA55 ranging from 6µg to 855µg. The highest concentration administered to patients was 15µg/ml and the highest infusion volume administered 185mL. In study 1, overall survival ranged at 6 and 12 months at 51% and 57%, respectively with a mean survival of more than 12 months for patients showing tumor response or disease control (68%). Pooled efficacy data from the other 2 studies showed overall survival at 6 months 51% and median survival 210 days, with rapid tumor necrosis observed in 50% of patients with a partial or a complete response. There were no evidence of systemic toxicity following intratumoral infusion nor detectable levels of MDNA55 systemically. There were no deaths attributed to MDNA55 and drug-related adverse events (AEs) were primarily neurological, mostly an aggravation of pre-existing neurological deficits characteristic of glioblastoma, with GMB or related to cerebral edema post infusion. The maximal tolerated dose in GMB patients was 240µg. Approximately 40% of treated patients had elevated systemic titers of anti-MDNA55 IgG antibodies, mostly directed against the PE moiety, for several months following infusion. These were not associated with any clinical sequelae. Conclusions: These studies illustrate the tumor selectivity and safety of MDNA55 for the intratumoral treatment of malignant gliomas. They also appear to suggest robust efficacy with favorable response rates and survival compared to historical comparators and a strikingly higher number of subjects with sustained outcomes than might have been anticipated. Furthermore, to the best of our knowledge, the side effects of MDNA55 mediated through its targeting of immunosuppressive MDSCs in the TME. Several features of MDNA55, make it a rational and attractive choice for the treatment of re-current GBM.

323 CPRIT Grantee Poster Session B
LSD1 inhibition alone and in combination with chemotherapy in Ewing’s sarcoma cell lines Ruoian Han, Salarius Pharmaceuticals LLC; D. Welch; E. Kahen; C. Cubitt; D. Reed
Introduction: Ewing Sarcoma (ES) is the second most common primary bone cancer affecting children and young adults. Despite advances in treatment that have led to survival rates of approximately 73% for localized disease, outcomes for patients with metastatic or recurrent ES remain poor. A distinguishing feature of ES is the presence of the EWS/FLI1 fusion in 85% of cases. The fusion has been shown to alter expression of a number of oncogenic genes. Mechanistic studies have demonstrated that EWS/FLI1, an HDAC co-repressor complex interacts with LSD1. The associated protein LSD-1 contributes to the repressive function by histone modifications. While reversible LSD1 inhibitors demonstrate single agent activity, in preclinical models, a system to evaluate combinations may be needed for optimizing effect in clinical trials. Methods: Here, we seek to confirm promising single drug activity and evaluate combination therapies using active chemotherapies currently utilized in ES care (4- HC, etoposide, SN-38, vincristine and doxorubicin) along with the LSD1 Inhibitors SP2509 and SP2577 and romidepsin, an HDAC inhibitor. We evaluated the combinations in high-throughput output screening platforms and well-established cell line models for ES (A-673, TC-32, RD-ES, TC-71). Taking into consideration past lessons learned from in vitro experiments, we designed stringent screening conditions that assess the candidate compounds and combinations at clinically-relevant concentrations and exposure times that mimic the in vivo pharmacokinetics in an effort to maximize the translational potential of these results to the clinical setting.
ABSTRACTS
Product Development research

suggest potentially promising opportunities for developing combination assays. FACS analysis verified the effect of RASP on apoptosis and cell-mediated networks and functional enrichment. Apoptosis was monitored analysis was performed using InSyBio Suite for the construction of miRNA (Ambion) and sequenced on the IonTorrent PGM platform. Bioinformatics

Express). The small RNAs fraction (<200 nt) was isolated with MiRVana DNA microarrays (One Array) on a Perkin Elmer platform (ScanArray (1

conjugate was used for intracellular localization studies. The RASP IC50

of human epidermis, at the molecular level.

present study was to evaluate the effect of RASP on HaCaT cells, a model previously established that the novel synthetic N1,N12-Bis(all-trans-

retinoyl)spermine (termed RASP) exhibits anti-cancer and anti-proliferative
depletion or the accumulation of the IDO1/TDO product kynurenine (Kyn)
cancers elevate tryptophan (Trp) catabolism in the tumor microenvironment

for targeted, tumor antigen-mediated delivery of GrB without the need

other immunotherapeutic approaches, rely on the delivery of the serine

protease granzyme B (GrB) to target cells resulting in a potent cytotoxic

effect. We developed a platform of novel human constructs

to inform further. Limma analysis identified important pathways involved in the functional enrichment of important pathways like TRIF-dependent toll-like receptor signalling, positive regulation of G1/S transition of mitotic cell cycle, SMAD protein signal transduction, negative regulation of TGFβ receptor signalling and negative regulation of cell growth. Consequently, several genes affect the induction of apoptosis and interface with different cell cycle phases. FACS analysis showed significant cell cycle arrest in G2 phase and DNA damage. Cell cultures at various conditions showed extensive mitochondrial breakdown and DNA fragmentation which is also supportive for the apoptotic path of cells after exposure to RASP. Conclusions: RASP treatment of melanoma and breast cancer cells provided with anti-proliferative and anti-cancer effects. Based on our previous studies and current results, we propose that RASP could be used further, in studies which could extend to melanoma and skin cancer treatment. RASP could provide the basis for further development of improved synthetic retinoid analogues without the deleterious effects of previous compounds in use.

CPRIT Grantee
Poster Session B

Illuminating the Role of Kynurenine in Cancer Progression and Treatment
Joseph Dekker, The University of Texas at Austin; N. Ashora; T. Triplett; K. Garrison; J. Blazcek; C. Karamitros; Y. Tanno; C. Lamb; E. Stone; L. Ehrlich; M. Zhang; M. Manfredi; G. Georgiou
Introduction: Cancer is the second leading cause of death in the United States and, despite progress in treatment options, there is a critical need for novel treatments that limit toxicity to healthy cells while targeting cancerous cells. Our immune system routinely identifies cancer cells and eliminates them prior to clinical intervention. To evade immune clearance, many cancers elevate tryptophan (Trp) catabolism in the tumor microenvironment (TME) by overexpressing the enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). This change in metabolism generates immune suppression in the TME, but whether the cause arises from Trp depletion or the accumulation of the IDO1/TDO product kynurenine (Kyn) remains highly controversial. Further, there is no known phenotype through aryl hydrocarbon receptor (AhR) activation. However, the functional role of this binding is poorly understood. This work aims to (1) determine Kyn’s effect on the immune system and (2) whether its depletion can relieve tumor burden. Methods: We observed the in vitro effects of Kyn addition on gene expression patterns and immune cell functionality in murine and human T lymphocytes. We tested the ability of a pharmacologically optimized enzyme, PEGylated kynureninase (Kynu) to safely degrade Kyn into multiple mouse cancer models to assess its effect on (1) tumor growth and (2) TME immune cell composition. Results: Exposing T cells to Kyn in vitro results in (1) gene expression changes consistent with Treg generation (FoxP3+CD4+ expression) and (2) an enhanced ability to repress naïve T cell proliferation, establishing Kyn as a key therapeutic target for relieving TME immune suppression. We next demonstrated that administration of Kynu potently inhibited tumor growth in several mouse models while also generating a significant increase in the infiltration and proliferation of polyclonal CD8+ lymphocytes. In treated animals, Kynu reduces Kyn concentration in the TME without affecting the concentration of Trp. Notably, we show that Kynu synergizes with clinically approved immune-checkpoint inhibitors, and that Kynu administration alone results in tumor regression when compared to the IDO1/TDO inhibitor, Epacadostat. Conclusions: Kyn accumulation in the TME independently plays a role in cancer’s immune evasion and directly induces Foxp3+Treg generation. Elimination of Kyn by an engineered human kynureninase, an ongoing project in our lab, will improve natural immune recognition of multiple tumor types. In this model, we also investigated the effect of Kynu on the TME, and found that Kynu administration, studying Kynu’s efficacy will illuminate details of Kyn’s mechanism of action, contributing critical information to diverse field of AhR-mediated immune regulation.

Dissecting the effect of a novel synthetic retinoid-polymamine conjugate on mRNA and miRNA expression profiles of HaCaT cells
Konstantinos Theofilatos, InSyBio Ltd; K. Grafanaki; C. Kontos; A. Korifiati; S. Mavroudi; D. Anastasakis; I. Skopanidis; G. Kyniakopoulos; D. Papaoannou; A. Scordilas; D. Drainas; C. Stathopoulos
Introduction: Synthetic retinoids with elaborate efficiency and minimum side effects have emerged as novel drugs. We have previously established that the novel synthetic N1,N12-Bis(all-trans-retinoyl)ispermine (termed RASP) exhibits anti-cancer and anti-proliferative activity, as well as limited toxicity and teratogenicity in rats. The aim of the present study was to evaluate the effect of RASP on HaCaT cells, an immortalized cell line of human epidermis, at the molecular level. Methods: A RASP-rodhamine conjugate was used for intracellular localization studies. The RASP IC50 (1μM) supplemented HaCaT culture media. Total RNA was analysed using DNA microarrays (One Array) on a Perkin Elmer platform (ScanArray Express). The small RNAs fraction (~200 nt) was isolated with MiRVana (Ambion) and sequenced on the IonTorrent PGM platform. Bioinformatics analysis was performed using InSyBio Suite for the construction of miRNA mediated networks and functional enrichment. Apoptosis was monitored using confocal microscopy for mitochondrial integrity and DNA damage assays. FACS analysis verified the effect of RASP on apoptosis and cell cycle regulation. Results: 1437 downregulated and 416 upregulated genes were detected during the mRNA expression analysis. In addition, 35 upregulated miRNAs targeting 1159 of the downregulated genes and 130 downregulated 336 upregulated were identified after target prediction analysis. The analysis with InSyBio Suite offers a unique miRNA target-prediction pipeline, which results in scored miRNA target sites in miRNAs with over 95% accuracy. Protein-protein interactions analysis was performed using the miRNA target-predicted genes, resulting in 31 downregulated and 2 upregulated genes which are involved in the functional enrichment of important pathways like TRIF-dependent toll-like receptor signalling, positive regulation of G1/S transition of mitotic cell cycle, SMAD protein signal transduction, negative regulation of TGFβ receptor signalling and negative regulation of cell growth. Consequently, several genes affect the induction of apoptosis and interface with different cell cycle phases. FACS analysis showed significant cell cycle arrest in G2 phase and DNA damage. Cell cultures at various conditions showed extensive mitochondrial breakdown and DNA fragmentation which is also supportive for the apoptotic path of cells after exposure to RASP. Conclusions: RASP treatment of melanoma and breast cancer cells provided with anti-proliferative and anti-cancer effects. Based on our previous studies and current results, we propose that RASP could be used further, in studies which could extend to melanoma and skin cancer treatment. RASP could provide the basis for further development of improved synthetic retinoid analogues without the deleterious effects of previous compounds in use.

Tegavivint (BC2059), a novel Wnt/β-catenin pathway inhibitor, demonstrates significant anti-tumor activity for osteosarcoma
Lamotton Nourma, Baylor College of Medicine; N. Rainusso; R. Shuck; L. Kurenbekova; J. Yustein
Introduction: Osteosarcoma is the most common bone cancer in children and adolescents. While outcomes have improved through the use of high dose chemotherapy, patients with metastatic disease still have extremely poor outcomes. It has been shown that the activity of Kyn, which is closely associated with osteosarcoma development and metastatic progression. Tegavivint (BC2059), a novel small molecule inhibitor of the Wnt/β-catenin pathway, has recently been reported to suppress the downstream activity of canonical Wnt signaling and induce apoptosis in AML and breast cancer (AML) cells. However, treatment resistance of its anti-tumor activity against solid tumors has not yet been reported. In this study, we investigated the anti-tumor activity of Tegavivint against human osteosarcoma cell lines and patient-derived xenograft (PDX) tumors in vitro and in vivo. Methods: In vitro: Human osteosarcoma cell lines (Sasco-2, LM7 and 143B) and PDX-derived cell lines (PDX22, PDX46, PDX54, PDX63 and PDX84) were treated with Tegavivint for 24 hours and the cell viability was evaluated by CCK-8 assay. In vivo: (1) Orthotopic placement of 1 x 10^6 LM7 cells was performed by injecting them into tibia of NSG mice and they were randomized to receive 5x/week intraperitoneal injections of Tegavivint or placebo when tumor volume reached 100 mm^3 (3) PDX83 tumor, which showed inherent resistance to doxorubicin in vitro, was implanted subcutaneously into the right dorsal flank of NSG mice. When the tumor volume reached 100 mm^3, they were randomized to receive 5x/week intraperitoneal injection of Tegavivint and/or doxorubicin. (3) PDX84 tumor, which was derived from the xenograft lung metastasis of PDX83, was dissociated into single cells and injected via tail vein into NSG mice. After one week, intraperitoneal injection of Tegavivint or placebo was initiated and livers were extirpated after 4 weeks of treatment to evaluate metastasis. Results: In vitro: Tegavivint showed anti-proliferative activity against all osteosarcoma cell lines tested in vitro in a dose-dependent manner. In vivo: (1) Orthotopic LM7 tumors were completely eradicated and lung metastasis was significantly suppressed in Tegavivint treatment group. (2) PDX63 tumor growth was significantly suppressed by Tegavivint alone and Tegavivint enhanced the anti-tumor activity of doxorubicin. (3) Lung metastasis was significantly suppressed by the treatment with Tegavivint. Conclusions: In summary, our pre-clinical data demonstrate that Tegavivint has promising therapeutic potential for primary and metastatic osteosarcoma. *This work was partially supported by Beta Cat Pharmaceuticals through the Product Development Award CP130058 from the Cancer Prevention and Research Institute of Texas (CPRIT).

Targeted granzyme B immunotherapy: A novel approach to deliver GrB to Fn14+ solid tumors
Linda Paradiso, Mirata BioPharma, LLC; L. Denning; Y. Tu; A. Ciafarditi; Y. Heung; K. Mohamedali; J. Winkles; L. Inge; T. Whitsett; M. Rosenblum
Introduction: All immune effector cells, including engineered T-cells and other immunotherapeutic approaches, rely on the delivery of the serine protease granzyme B (GrB) to target cells resulting in a potent cytotoxic (apoptotic) effect. We developed a platform of novel human constructs for targeted, tumor antigen-mediated delivery of GrB without the need for effector cells. These bivalent constructs incorporate scFv proteins

Poster Session B

PRODUCT DEVELOPMENT RESEARCH
that bind to cell-surface antigens as Targeted GrB Immunotherapeutics (TGIs). Our initial focus is GrB-Fc-IT4 (MRT-101), a dimeric, bivalent construct that binds to the TWEAK receptor, Fn14, with growth factor-inducible protein 14 (Fn14). This receptor is highly over-expressed in many solid tumors including non-small cell lung cancer, (NSCLC), triple-negative breast cancer (TNBC) and melanoma. High Fn14+ expression is a negative prognostic factor for disease recurrence and survival. Methods: GrB-Fc-IT4 was value in comparison to human NMT1 and NMT2 expressing Fn14, MDA-MB-231 (TNBC), 5/group, at doses of 4, 8 and 20 mg/kg, and in an Fn14+ NSCLC patient-derived xenograft (PDx) model at 20 mg/kg, 6/group; all doses administered IV every other day for 5 total doses. A pharmacokinetic (PK) study was conducted in mice at 10 mg/kg single-dose doses using many false positive predictions. Methods: To overcome this problem, in the present work, we utilized InSyBio's Suite (https://www.insybio.com/pages/suite) in order to locate the genes whose role in the underlying biological networks is significantly altered after the application of different types of IR i.e. high-LET alpha particles and proton radiation (Gene Expression Omnibus Datasets: GSE23899 and GSE21059). These types of radiations are relative to the evolving use of particles for the efficient RT. We pre-processed all datasets to estimate missing values with the k-Nearest Neighbours imputation method, normalized the data, and then used the differentially expressed genes according to their biological condition, e.g. normal samples, cancer samples radiated low dose, etc. Next, for every biological condition, a gene-co-expression network was constructed using a Pearson correlation based method with adaptive threshold for adding edges between two nodes. As a next step, we obtained the minimal co-expression networks were compared using a Pagerank based method in order to identify network modules whose role in the biological networks is significantly altered in different radiation therapy setups. Finally, the uncovered genes were filtered to keep only differentially expressed ones and scored according to their importance. The identified gene lists were further used to represent their corresponding protein-protein interaction networks, and to functionally annotate them with Gene Ontology and KEGG terms. Results: The network-based bioinformatics analysis resulted in short lists of genes whose role in the underlying biological networks is significantly altered when applying alpha particles and proton radiation of various setups. These lists except from genes whose connection with ionizing radiation has already been studied such as RAB31, include other genes such as KLF5 and GP9. Conclusions: The identification of genes and their role(s) in the radiation response biological network and how it is altered after the application of different types of IR could be the first step towards deeper understanding the molecular mechanisms of radiation response including radiation-induced immune response and evolution of carcinogenesis.

328 Poster Session B Development of a precision oncology approach for the treatment of lymphomas and other cancers Donald Stewart, Omm Scientific Inc; J. Mackey; R. Heit; L. Berthiaume

Introduction: Myristoylation critically regulates membrane binding of numerous proteins and signal transduction. It is catalyzed by two ubiquitously expressed N-myristoyltransferases (NMT1 and NMT2) in mammalian cells. The current understanding is NMTs are overexpressed in cancer. Methods: Using bioinformatic tools, bisulfite sequencing, HDAC and DNA methylation inhibitors, rationale drug design on first-in-kind target (NMT), click chemistry, cancer cell toxicity assay in vitro using first-in-kind lead candidate and in vivo using xenografts, Western blotting and other biochemistry and immunohistological assays, we show that loss of Nkd1 functionality leads to derepression/activation of the Wnt pathway. Loss of Nkd1 functionality leads to derepression/activation of the Wnt pathway and explains in part the high prevalence of NMT2 loss in numerous cancers. We exploit this NMT2 loss to selectively kill NMT2-deficient lymphoma cells with a potent first-in-class NMT inhibitor, PCLX-001, in vitro and in three B-cell lymphoma xenograft models, and spare normal cells (which have two NMTs). In addition, we have developed a companion diagnostic test using proprietary monoclonal anti-NMT antibodies that enable the identification of patients with NMT2-deficient cancer. Methods: Using FACS analysis of primary cell lines and FACS analysis of the epigenetically induced essentiality at one of two NMT loci to inhibit the remaining NMT1 with PCLX-001 represents a novel "synthetically toxic" approach to lymphoma therapy.

329 Poster Session B Deciphering the impact of radiation therapies at molecular level using biological network based bioinformatics Konstantinos Theocharis, InSyBio Ltd; K. Tatsi; S. Mavroudi; A. Georgakilas

Introduction: Understanding the interaction of different types of ionizing radiation (IR) with healthy and cancer biological samples is an open problem in radiation biology whose solution could be a step towards personalized radiation therapy (RT) and counteract IR-related mechanistic insights on radiation-induced carcinogenesis and toxicity. However, using simple differentially expression techniques for the analysis of relative transcriptomics datasets generated after applying different types of IR therapies on cancer tissues results in a large number of genes including many false positive predictions. Methods: To overcome this problem, in the present work, we utilized InSyBio's Suite (https://www.
release of hydrophobic drugs, such as Paclitaxel. We have also achieved a high loading of Paclitaxel into the LiNPs, with low drug leakage and high stability of the drug. Preclinical trials of MTS assays of drug release showed that a loaded LiNPs demonstrate effective cancer killing capability, while retaining low toxicity to healthy cells. **Conclusions:** The innovative LiNPs technology being developed by NanoHybrids, Inc. will allow more of the thousands of new cancer drugs in development to overcome solubility limitations and reach the clinic, giving cancer patients more treatment options and potentially stronger GvL effect in children with high-risk leukemia who lack a matched donor.

**Poster Session B**

**Impact of Post-Transplant Infusion of Donor T Cells Genetically Modified with Inducible Caspase 9 Safety Switch (BPX-501 Cells) on Outcomes of Children with Leukemia given Alpha Beta T-Cell Depleted HSCT**

*Vincent O’Neill, Bellicum Pharmaceuticals, Inc.; P. Merli; A. Bertaina; T. Galavera; M. Algeri; F. Locatelli.*

**Introduction:** HLA-haploidentical allogeneic hematopoietic stem cell transplant (haplo-HSCT) offers an option for children with acute leukemia who lack an HLA-identical donor. T cell depletion reduces the risk of GVHD, but leads to delayed immune reconstitution, predisposing to serious infections and leukemia relapse due to the lack of a graft-versus-leukemia (GvL) effect. To address these challenges, we have infused modified donor T cells (donor lymphocytes modified with the iCasp9 suicide gene) after αγδ T-cell depleted haplo HSCT to facilitate immune reconstitution and GvL. BPX-501 T cells are genetically modified with the iCasp9 safety switch and a truncated CD19 marker. In the event of GvHD, the switch is activated by an infusion of the drug rimiducid resulting in rapid T cell apoptosis and GvHD reversal. **Methods:** A prospective Phase I/II study enrolling children with hematopoietic disorder who lack a matched donor. 38 patients have been enrolled and treated with αγδ TCR depleted haplo HSCT after a myeloablative regimen followed by BPX-T cell infusion to date; 24 had ALL, and 14 AML (21% CR1, 79% CR2). Median follow-up is 11 months (range 3-24). **Results:** All patients engrafted with no secondary graft failure. Median time to neutrophil and platelet recovery was 16 days (range 8-33) and 11 days (range 7-19), respectively. With a median follow-up of 11 months (range 3-24 months) there was no evidence of infection and incidence of grade II and III acute GVHD was 12% and 12.0%. All aGVHD resolved (5 Grade I skin, 5 Grade II skin, 2 Grade III GI). One child received rimiducid to treat steroid-resistant Grade II skin with complete resolution in 24 hours. There were 3 cases of chronic GVHD, 2 were mild; 1 severe and fatal in a patient whose donor had V2V3 reactivated during mobilization. **Conclusions:** Engraftment was brisk and T cell recovery normalized by 6 months. Overall incidence of severe aGVHD was low and rimiducid infusion successfully activated the safety switch. Cumulative incidence of NRM compares favorably to historic controls. The data suggest that BPX-501 T infused after αγδ T-cell depletion results in a rapid immune reconstitution and a potentially stronger GV effect in children with high-risk leukemia who lack a matched donor.

**Poster Session B**

**Antitumor activity of Bcl-2 DNAbilize™ antisense in non-Hodgkin’s lymphoma**

*Ana Tari Ashizawa, Bio-Path Holdings, Inc.; Y. Gutierrez-Fuente; R. Ford; G. Lopez-Berestein.*

**Introduction:** Aggressive non-Hodgkin’s lymphoma (NHL) progresses rapidly. It makes up about 60% of all NHL cases in the United States. The chemotherapy regimen R-CHOP could cure up to 70% of patients with aggressive NHL, but about 30% of patients relapse from R-CHOP within 2 years of initial treatment. Novel therapies are urgently needed for patients with relapsed, aggressive NHL. Bcl-2 is a potential therapeutic target because high expression of Bcl-2 has been correlated with adverse prognosis for NHL patients. The DNAbilize™ antisense technology has been well tolerated in clinical and preclinical studies and has been associated with the clinical utility of DNA antisense: drug instability, drug delivery, and non-specific toxicity. The DNAbilize™ antisense, which is a combination of an uncharged P-ethoxy antisense backbone and a neutral liposome delivery vehicle, was utilized to develop BP1002 to inhibit Bcl-2 expression. **Methods:** First, we investigated the potential adverse effects of BP1002 in mice. Normal CD-1 mice were intravenously injected with BP1002 at doses of 7.5, 15 or 30 mg/kg, twice weekly for 4 weeks. Mouse body weight, hematological parameters, liver and kidney functions, and histopathology were used to examine BP1002 potential toxicity. Second, we studied the anti-tumor activity of BP1002 in NHL cell lines. The viability of NHL cells after incubation with BP1002 was determined by the sulforhodamine B cytotoxicity assay. Third, we studied the activity of BP1002 in extending the survival of severe combined immunodeficiency (SCID) mice implanted with NHL xenografts. SCID mice bearing NHL xenografts were intravenously injected with 20 mg/kg of BP1002 or liposome-incorporated control oligodeoxynucleotide twice weekly until they were moribund. **Results:** BP1002, even at 30 mg/kg, was not toxic to normal mice. BP1002 did not decrease mouse body weight or kidney functions. BP1002-treated tumor-bearing mice did not show drug-related toxicity in major organs examined. On the other hand, BP1002 exerted anti-tumor activity; BP1002 decreased the viability of NHL cells and extended the survival of mice bearing NHL xenografts. At 200 micrograms/mL, BP1002 decreased 35% viability in 10 of 13 NHL cell lines. All untreated mice and control mice were moribund by 17.5, but only 40% of BP1002-treated mice were moribund. **Conclusions:** Similar to our other DNAblize™ antisense drugs, BP1002 is safe and can be delivered systemically. Moreover, BP1002 suppresses the viability of NHL cells in vitro and in vivo, indicating that BP1002 is a novel potential therapeutic for aggressive NHL.

**Poster Session B**

**Metallic ions: A promising platform technology against cancer**

*Zsolt Keresztesy, Ion Biotechnology (USA); D. Stone; J. Kennedy.*

**Introduction:** Ionic metallopharmaceuticals have demonstrated anti-cancer activity, such as cisplatin in chemotherapy which uses the platinum ion. J. W. Kennedy invented a platform technology based on other ionic metals, which is theorized to exploit differences in metabolic cycles of healthy and cancer cells. The platform utilizes proprietary blends of metallic ion coordination complexes in aqueous solution. The first drug candidate, ION-ZC1, is based on copper (II) and zinc (II) complexes of different functionalized oligonucleotides. The anti-cancer toxicity and efficacy, are currently underway in preclinical models by Ion Biotechnology. **Methods:** Ant-tumor efficacy of ION-ZC1 was tested in a syngeneic mouse melanoma model by subcutaneously injecting B16 melanoma xenografts into the right flank of C57BL/6 mice. Tumors were then randomized (n=10/group) and topically treated with 17% ION-ZC1 in a cream vehicle, imiquimod, or control. Anti-tumor efficacy of ION-ZC1 was evaluated by tumor dynamics as presented by tumor volume over time. Measurement of acute toxicity of ION-ZC1 was performed by 0.2 mL tail-vein injection in mice (same strain) with five concentrations ranging from 0.78% to 12.5% using a baby braneul system. Mice were monitored for 14 days post injection and analyzed for survival, body weight, blood composition, organ weight, and pathology. **Results:** ION-ZC1 suppressed tumor volume in B16 mouse melanoma more effectively than imiquimod. ION-ZC1 was not toxic at the four lowest doses. At the highest dose, two mice died after injection (cause unknown), there was minor liver toxicity, and weight gain in liver, brain, and kidneys. **Conclusions:** These pilot studies suggest ION-ZC1 may be an effective and non-toxic treatment in B16 mouse melanoma. Ion Biotechnology, a company formed this year in Texas, is developing this and other metallic ion coordination complexes as candidates for novel anticancer therapies.

**Poster Session B**

**Challenges in manufacturing scale-up of plasmonic gold nanorods: Bringing photothermal therapy to the clinic**

*Len Pagliaro, Siva Therapeutics Inc.; J. Harris; M. Butman.*

**Introduction:** Siva Therapeutics Inc. and NanoHybrids Inc. are developing a simple, safe, and effective cancer treatment - Targeted Hyperthermia™ - for photothermal therapy. Using systemically injected SivaRods™ precision gold nanorods coupled with a SivaLum™ infrared light engine, therapeutic heat is generated within solid tumors. Heat has been shown to destroy cancer cells, stimulate the immune system, inactivate cancer stem cells, and improved drug efficacy through increased perfusion. Targeted Hyperthermia provides precision heating of tumors with minimal collateral damage, and promises to be a valuable adjunct to drug therapy. While awareness of the therapeutic value of hyperthermia has been in the cancer community for many decades, implementing practical, safe, and cost effective hyperthermic therapies has been challenging. Nanotechnology has provided key tools for targeting heat to tumors. Hyperthermia has demonstrated significant in vivo activity in both animal models and recently in the clinic. **Methods:** An important hurdle for photothermal therapy has been scaling up the production of plasmonic gold nanorods to pilot batch size, while maintaining the ideal absorption spectra and uniformity. SivaRods are currently undergoing batch scale-up studies, including full physico-chemical characterization, absorption spectra and uniformity. SivaRods are currently undergoing both animal models and recently in the clinic. **Results:** The results of pilot batch scale-up studies, including full physico-chemical characterization, will be shown. Additionally, Siva is developing a second-generation light engine with the ability to illuminate regions of ~10 cm in diameter with high intensity infrared light to excite nanorods that have concentrated in tumors. **Conclusions:** Together, these advances have made nanotechnology-enabled photothermal therapy more practical, safe, and cost-effective than was previously possible. Targeted Hyperthermia is currently in preclinical testing and unapproved by the FDA; it is anticipated that it will be a Class 3 PMA medical device.
ABSTRACTS

336 CPRIT Grantee Poster Session A
Postpartum HPV Vaccination of Young Women Delivering at a Healthcare Center in Southeast Texas: A Program Assessment
Abbey Berenson, The University of Texas Medical Branch at Galveston; J. Hirth; R. Rupp; K. Sarpong
Introduction: Effective interventions are needed to address the low rate of human papillomavirus (HPV) vaccination in the United States, particularly among young women. Counseling and offering the vaccine to postpartum women could be an effective strategy to increase uptake among those who did not complete the 3-dose series at an earlier age. The purpose of this evaluation was to assess the effectiveness of a multi-component program designed for postpartum women that used patient navigators and reminders for follow-up visits to improve completion of the HPV vaccine series. Methods: All HPV vaccine-eligible women (N=1,832) were educated about it by specially trained vaccine coordinators within 24 hours of delivery. They were offered the opportunity to initiate or complete the series at no cost to them through CPRIT funding. Follow-up appointments to receive subsequent doses were coordinated with a postpartum visit or at the pediatrician’s office where their newborn received care. Women who missed an appointment were called by a vaccine coordinator to reschedule. We evaluated completion rates among participants to determine the effectiveness of this approach. Results: A total of 1,340 (73.1%) eligible women agreed to receive the HPV vaccine on the postpartum unit. There were 1,144 women who received their first dose, 102 that received their second dose, and 94 that received their third dose during their hospitalization or shortly thereafter. Of the 999 women who initiated and were eligible to receive the third dose at the time of this analysis, the series completion rate was 84.8%. Only 9.2% of women were lost to follow-up and 6.0% were overdue for the final dose of the vaccine at time of analysis. Conclusions: This program achieved a HPV vaccine series completion rate much higher than reported averages for the US and Texas and may be an effective way to reach underserved women who did not get vaccinated at a younger age.

337 CPRIT Grantee Poster Session B
Medical Student Willingness to Offer the HPV Vaccine by Vaccination Status
Abbey Berenson, The University of Texas Medical Branch at Galveston; J. Hirth; R. Rupp; Y. Kuo
Introduction: The HPV vaccine is an underutilized tool for preventing cancers. Multiple studies have shown that provider recommendation is the best predictor of HPV vaccine uptake. Additionally, a provider’s own attitude about the vaccine is a strong predictor of recommendation behaviors. We therefore sought to determine if a provider’s personal vaccination status affects willingness to recommend the HPV vaccine. Methods: An anonymous, voluntary, 1-page survey was administered to multiple groups of third-year medical students from November 4, 2015 to November 23, 2016 during obstetrics/gynecology clinical rotations at the University of Texas Medical Branch in Galveston. The survey aimed to assess knowledge and attitudes about HPV and the HPV vaccine. Results were analyzed using chi-square for bivariate analyses. Fisher’s exact tests evaluated differences for any outcomes with cell counts ≤5. Results: A total of 231 students completed the survey and provided information about their personal HPV vaccination status. A higher frequency of students were ≤25 years old and female. Most (58%) were unvaccinated. Vaccinated medical students were more often ≤25 years old and female. Knowledge did not vary by vaccination status. Significant differences (p<0.05) in frequency were observed between vaccinated and unvaccinated students for: a preference to wait until a child is 15-16 years old to recommend the vaccine; willingness to discuss the vaccine when patients come in for other problems, including chronic conditions; and willingness to recommend the vaccine for 9–10 year olds. Conclusions: Even though medical students are a well-educated population involved in healthcare, there is still a need for interventions to increase HPV vaccine uptake among them. Vaccinated medical students appeared to have a stronger commitment to HPV vaccination at every eligible patient encounter than unvaccinated students. Campaigns focused on increasing HPV vaccination among medical students might be an effective way to increase the number of HPV vaccines administered at the CDC-recommended ages.

338 CPRIT Grantee Poster Session A
Quitxt: A Text-Based Smoking Cessation Service for Young Adults in South Texas
Patricia Chalela, The University of Texas Health Science Center at San Antonio; A. McAlister; G. Galion; E. Munoz; C. Despres; D. Akopian; S. Kaghiyan; A. Fernandez; R. Diaz; A. Ramirez
Introduction: Smoking among Latino young adults (18-29) in South Texas is high (23.2% to 25.7%), representing a serious public health problem. Yet few are reached by services to help them quit smoking. Young adults are heavy users of mobile devices for texting and access to mobile media. These have an extraordinary potential for assisting smoking cessation by providing peer modeling and eliciting social reinforcement for behavior change. We present preliminary results from a bilingual text messaging and mobile media service to help young adults quit smoking. Methods: We constructed a bilingual textual and mobile media system that was promoted in South Texas via social media advertising and other recruitment channels. The ads, which featured couples with different cigarettes (disguised as savings or costs of success) and styles (cowboy, metro/urban, geek, punk and graphic novel), asked potential participants who showed interest in quitting smoking to text a code to our system corresponding to the channel of recruitment. Text messages include links to web pages with additional content and YouTube videos with peer modeling of reasons and skills to quit smoking. Results: Results showed that enrollments were achieved for 798 participants with a mean age of 29.3 and 55% were below the age of 30. More men (57%) than women (43%) enrolled and 36% identified themselves as Hispanic or Latino. The mean number of cigarettes consumed per day was 11.5. Seven-month texted follow up found that 21% (171) of the enrollees reported abstinence at that point. This is consistent with high rates of success found in studies of telephone counseling for young adults and confirms that text and mobile media service specifically designed for young adults provide a feasible and cost-effective approach to promoting cessation. Conclusions: Results provide evidence that young adult smokers in South Texas can be reached via mobile media service. The anticipated outcome is a scalable, culturally relevant, evidence-based and cost-effective service with broad national reach to help young adult Latinos stop smoking, taking the potential to reduce health care costs, reduce chronic disease burden and improve quality of life among this young, fast-growing, at-risk population.

339 CPRIT Grantee Poster Session B
Tobacco Dependence Education for Staff and Clinicians at Behavioral Health Centers: Knowledge Gained and Lessons Learned
Bryce Kyburz, Austin Travis County Integral Care; S. Buoy; D. O’Connor; I. Martinez Leal; W. Wilson; V. Correa-Fernández; T. Stacey; L. Reitze
Introduction: Cigarette smokers significantly increase their cancer risk. Overall, 14% of adults in Texas smoke. However, smoking is more common among mental and behavioral health center clientele, with rates ranging from 40-75%. Many health clinicians in these settings lack the knowledge and resources to address tobacco use. Taking Texas Tobacco Free (TTTF) is a collaboration between the University of Houston (UH) and Integral Care (IC) to assist behavioral health clinics across Texas in the adoption of a multi-component program that includes providing education on tobacco dependence to all staff and clinicians; cessation resources; specialized training to clinicians and prescribers; and tobacco-free workplace policy development and implementation. This presentation focuses on the education provided to non-clinicians (staff with non-clientile contact) and clinicians (direct clientele contact) by outlining knowledge gained via on-site vs webinar-based training and lessons learned in the transition between the modalities. Methods: Since 2013, 1- (staff) or 2- (clinicians) hour educational sessions have been provided to almost 5,000 employees working within hundreds of behavioral health clinics. Trainings were conducted by tobacco cessation specialists from UH and IC. A 10-item knowledge test was administered pre- and post-trainings. Initial funding (PP130032) allowed on-site trainings, and dissemination funding (PP160081) piloted live webinar-based administration of trainings. Training content was unchanged. Results: Knowledge increase from pre- to post-training was 24.1% for the on-site vs 23.9% for the webinar-based non-clinical staff trainings. Knowledge increase was 24.0% for the on-site vs 19.1% for the webinar-based clinician trainings. The difference between modalities in knowledge gained was statistically significant for clinician trainings. However, this difference was not statistically significant for <1 additional correct response on the knowledge test. Each presentation modality had challenges and benefits, which are reviewed in conjunction with knowledge gain results. Conclusions: TTTF has provided behavioral health staff with an evidence-based tobacco control program that has evolved over time. Movement from on-site to on-line tobacco dependence education trainings for employee stakeholders was one modification. This change made training more efficient and less costly with little sacrifice to knowledge increases among non-clinical staff. Although there was improvement in knowledge gain among staff trained by clinicians, the magnitude of the difference may not be significant in practice. This presentation covers the specifics of training implementation, pros and cons of on-site vs on-line trainings, and lessons learned from the transition.

340 CPRIT Grantee Poster Session A
MHMR Tarrant County: Providing Nicotine Recovery Programs to Behavioral Health and the Community
Lawrence Carter, Mental Health Mental Retardation of Tarrant County; C. Johnson-Harris
**Abstracts**

**Prevention**

Communities. We provide patches, gum and lozenges to those who chose Replacement Therapies in Behavioral Health clinics and those in the products. Our goal has been to encourage use of FDA approved Nicotine with nicotine addictions and health related issues caused by nicotine speaking Community Health Workers program. Those entering the program, 60% (871) completed the smoking cessation or group sessions—whichever was more convenient for the person. Of 6,338 Fagerstroms administered by staff within the various clinics. Of nicotine/tobacco users in 16 clinics. This information was collected from resources for the participants are set up to view and use. To determine actual decrease of CO in their system. Also, MHMR Tarrant’s NRP provides education to the community by participating in community health fairs. At these events, display tables with pamphlets and outside locations. In the Tarrant County community. The nicotine user’s individualized needs are determined upon entering treatment by administration of the Fagerstrom and NHINES smoking surveys which determine initial level of use. Both surveys are administered at the start and completion of treatment to measure decreased use of nicotine products. Individuals’ Carbon Monoxide level in their lungs is tested throughout the 8 sessions, to determine actual decrease of CO in their system. Also, MHMR Tarrant’s NRP provides education to the community by participating in community health fairs. At these events, display tables with pamphlets and outside resources for the participants are set up to view and use. **Results:** Within the last year in the previous program, there were 3,988 self-reported nicotine/tobacco users in 16 clinics. This information was collected from 6,338 Fagerstroms administered by staff within the various clinics. Of the self-reported tobacco users 1,326 individuals reported a willingness to quit. During this reporting period 1,454 (37%) of the self-reported nicotine/tobacco users were enrolled as new program participants. These individuals received services in the form of individual sessions or group counseling. Recovery was more prominent for the participants those entering the program, 60% (871) completed the smoking cessation program. **Conclusions:** Primary prevention with the NRP is helping those with nicotine additions and health related issues caused by nicotine products. Our goal has been to encourage use of FDA approved Nicotine Replacement Therapies in Behavioral Health clinics and those in the communities. We provide patches, gum and lozenges to those who chose to refrain from using nicotine products. **Poster Session B**

**Developing and Disseminating a Family Health History-based Cancer Genomics Training Program for Hispanic and English Speaking Community Health Workers**

Lei Shih Chen, Texas A&M University; S. Zhao; Y. Yeh; K. Nimmons

**Introduction:** Cancer, a genomic disease, is the second leading cause of death in Texas. According to the Centers for Disease Control and Prevention (CDC), genetic counseling (GC) serves as an important genomics tool for providers to identify clients’ personalized cancer risk. Later, cancer prevention strategies can be tailored to clients based on their individualized cancer risk. Such FHH-based cancer genomics service has been shown to be an effective approach for cancer prevention. Due to the shortage of genetic counselors and difficulties in reaching underserved communities, community health workers (CHWs) are the ideal candidate to provide FHH-based cancer genomics services. Yet, CHWs have not been trained in this topic. To fill this gap, this CPRIT-funded study aimed to develop and disseminate the first FHH-based cancer genomics training program for CHWs in Texas. **Methods:** Our program has two phases. In the development phase, we proposed the FHH-based cancer genomics training curriculum for CHWs in Texas. In the implementation and dissemination phase, partnering with CHW training centers in Texas, we proposed to implement, evaluate, and disseminate the FHH-based program in both workshop and Web-based formats to all CHWs in Texas. **Results:** The cancer genomics training curriculum was developed and reviewed by a research team of health educators, a CHW instructor, geneticists, genetic counselors, and physicians. It was based on the Social Cognitive Theory, the Diffusion of Innovations Theory, and the Theory of Planned Behavior and addressed CHWs’ education level, background, and work setting. Given that Texas has a large Hispanic population, the curriculum was translated to Spanish to reach out to more CHWs. The final version of the curriculum was approved by the Texas Department of Health Services. The staff were then certified to conduct education hours for CHWs. We plan to pilot both English and Spanish curriculum in early Fall 2017. Based on the findings, the curriculum will be revised, delivered, and disseminated to all CHWs in Texas. Data from the clients served by CHWs will be collected. **Conclusions:** This FHH-based cancer genomics training program is currently in the development phase. Program evaluation data will be presented at the conference. This study is anticipated to increase CHWs’ competencies in cancer genomics, which will in turn, reduce cancer mortality and morbidity rates in Texas.
344 **CPRIT Grantee Poster Session A**

**Factors Impacting Tobacco Cessation in Behavioral Health Facilities:** A Qualitative Analysis
Isabel Martinez Leal, University of Houston; H. Okamoto; S. Shree; B. Kyburz; W. Wilson; V. Correa-Fernández; D. O’Connor; L. Reitzel

**Introduction:** Tobacco use is the leading cause of preventable death worldwide and is linked to 40% of all diagnosed cancers. In particular, smoking rates are 2-3 times higher for behavioral health consumers in the US compared to the general population. To address this disparity, it is essential to identify the factors hindering the adoption of tobacco cessation interventions in behavioral health facilities. Taking Texas Tobacco Free (TTTF) is a collaboration between the University of Houston and Integral Care delivering a multi-component tobacco-free program consisting of: education on tobacco dependence to all staff and clinicians, specialized training to clinicians and prescribers, tobacco-free policy development and implementation, integration of tobacco-use assessment and treatment resources, and community engagement and outreach to behavioral health clinics across Texas to treat tobacco use and address second-hand smoke exposure. Here, we identify the factors hindering the adoption of tobacco cessation interventions in participating behavioral health facilities to inform more effective intervention design and implementation efforts.

**Methods:** An explorative qualitative study was undertaken between January and April 2017. Three focus groups (ns = 6, 9, and 13) were conducted with clinicians and managers at 3 facilities before program implementation. Thematic analysis and constant comparison were used to code, categorize and summarize data into themes.

**Results:** Data analysis yielded 5 themes impacting tobacco cessation efforts: 1) policy parameters and applicability; 2) organizational culture: values and practices; 3) tailoring program to suit community center; 4) staff attitudes towards clients and tobacco-use; and 5) internal conflicts of addiction. These themes reflect factors on the socioeconomic-political system, organizational, community, interpersonal and personal levels. They interact across levels and are barriers to the implementation of tobacco cessation interventions.

**Conclusions:** Because behavior change is both affected and affected by various levels of influence, tobacco control is a multidimensional issue. Reducing or quitting tobacco among behavioral health consumers requires addressing barriers across different levels of influence – systemic, organizational, community, interpersonal and personal levels. This study identified clinicians’ perceptions of the various factors influencing tobacco cessation efforts at behavioral health centers. These findings contribute to the development of effective tobacco health interventions that consider reciprocal, multilevel influences impacting tobacco dependence at these different centers, thus enhancing the effectiveness and sustainability of the TTTF program.

345 **CPRIT Grantee Poster Session B**

**Implementation of a HPV Vaccination Program in UTMB Pediatric Clinics:** What are patient navigator and provider perceptions of remaining barriers to vaccination
Jacqueline Hirth, The University of Texas Medical Branch at Galveston; E. Dinehart; L. Cofie; R. Rupp; Y. H. Cofie

**Introduction:** Human papillomaviruses (HPV) are the most common sexually transmitted infections in the US. Persistent infection can cause several cancers, including: oropharyngeal, cervical, vaginal, vulvar, anal, and penile cancers. Vaccination with the HPV vaccine is expected to reduce the burden of these cancers. In particular, Texas has experienced a high rate of cervical cancer cases, yet has had suboptimal rates of vaccination since it was introduced. In order to address the low vaccination rates, an HPV Vaccination Program utilizing patient navigators (PNs) was implemented in 2 pediatric clinics. The purpose of this study was to evaluate PN and provider perceptions of the program and remaining barriers to vaccination.

**Methods:** We developed a multi-level data collection strategy, still in progress, consists of: (1) focus groups with primary care providers/staff; (2) interviews with Liver clinic providers/staff; (3) interviews with primary care providers based on high or low individual screening rates; and (4) interviews with patients at 3 different stages of the screening continuum: antibody (Ab)+ without confirmatory HCV RNA, RNA+ without a Liver Clinic appointment, and Liver clinic patients. Interview and focus group domains include: knowledge of hepatitis C and available treatments; experiences with the testing and referrals, perceived and/or experienced stigma toward people with hepatitis C, and access to services and treatment.

**Results:** Preliminary data reveal: (1) Primary care providers and staff are familiar with hepatitis C screening guidelines but lack understanding of specific procedural requirements, e.g. which tests are required before treatment evaluation; ignoring EMR reminder due to lack of knowledge and/or priority clinical concerns; and concerns about delays and rejection of referred patients. (2) Providers and staff at Liver clinic report patients are eager to learn about hepatitis C and treatment; the vast majority of patients are medication compliant; recommending vaccination is primarily related to time involved in medication authorization from insurance providers (especially Texas Medicaid); and providers are pleased with clinic modifications to increase efficiency, e.g. expansion of clinic space and staffing. (3) Despite understanding about modes of hepatitis C transmission, Liver clinic report fear of infecting family members and gratitude for access to medications, and relief about being cured.

**Conclusions:** Qualitative evaluations of providers’ and patients’ experiences with hepatitis C screening and treatment reveal areas of success and opportunities to enhance prevention at patient-, provider-, and system-levels.

346 **CPRIT Grantee Poster Session A**

**Patient and provider barriers to hepatocellular carcinoma prevention through hepatitis C screening and treatment in a county integrated safety net health system**
Robin Higashi, The University of Texas Southwestern Medical Center; L. Quirk; S. Lee; M. Jain; B. Turner; A. Singal

**Introduction:** Hepatitis C-related cirrhosis is the most common risk factor for hepatocellular carcinoma (HCC). Hepatitis C treatment is the most effective method for HCC primary prevention to reduce future HCC burden in Texas; however, effective implementation of an HCC prevention program through hepatitis C screening and treatment of baby boomers (born 1945-65) in a county integrated safety net system poses several challenges. As part of a national study to evaluate screening program discontinuance, Parkland primary care clinics from 2015-2017 indicates uneven and suboptimal uptake of the intervention: overall, < 35% of eligible baby boomers were tested for hepatitis C despite intensive education, training, and efficacious medical records reminders. This study aims to identify intervention barriers and facilitators to identify strategies that can enhance implementation of HCC prevention.

**Methods:** A multi-level data collection strategy, still in progress, consists of: (1) focus groups with primary care providers/staff; (2) interviews with Liver clinic providers/staff; (3) interviews with primary care providers based on high or low individual screening rates; and (4) interviews with patients at 3 different stages of the screening continuum: antibody (Ab)+ without confirmatory HCV RNA, RNA+ without a Liver Clinic appointment, and Liver clinic patients. Interview and focus group domains include: knowledge of hepatitis C and available treatments; experiences with the testing and referrals, perceived and/or experienced stigma toward people with hepatitis C, and access to services and treatment.

**Results:** Preliminary data reveal: (1) Primary care providers and staff are familiar with hepatitis C screening guidelines but lack understanding of specific procedural requirements, e.g. which tests are required before treatment evaluation; ignoring EMR reminder due to lack of knowledge and/or priority clinical concerns; and concerns about delays and rejection of referred patients. (2) Providers and staff at Liver clinic report patients are eager to learn about hepatitis C and treatment; the vast majority of patients are medication compliant; recommending vaccination is primarily related to time involved in medication authorization from insurance providers (especially Texas Medicaid); and providers are pleased with clinic modifications to increase efficiency, e.g. expansion of clinic space and staffing. (3) Despite understanding about modes of hepatitis C transmission, Liver clinic report fear of infecting family members and gratitude for access to medications, and relief about being cured.

**Conclusions:** Qualitative evaluations of providers’ and patients’ experiences with hepatitis C screening and treatment reveal areas of success and opportunities to enhance prevention at patient-, provider-, and system-levels.
**Primary Prevention**

and provider interviews about HPV vaccination. Additionally, the study team developed an AD booklet with supplemental materials using the Centers for Disease Control and Prevention’s “Your School and You: A Guide to Cancer Prevention” curriculum, the Immunization Schedule for Preteens and Teens, and The Community Guide. Clinic facilitators will deliver four monthly AD sessions to providers followed by two sessions to develop a strategic plan. Each session will last 30-60 minutes and give providers continuing education credit. The two sessions cover the following themes: (1) understanding the burden of HPV infection and disease; (2) evidence-based strategies to HPV disease prevention; (3) talking about HPV vaccine to patients; and (4) strategies to improve HPV vaccine coverage. Results: Eleven clinics in five Texas counties are participating in the PDI. Two clinic facilitators are collecting baseline data and implementing the PDI in two distinct territories. Reports summarizing baseline data have been shared with the lead provider at four participating clinics, while baseline data is being finalized for four other sites. Conclusions: We expect that AD will empower providers to make a strong recommendation for the HPV vaccine and increase HPV vaccine initiation and completion rates in these rural clinic settings. Thus far, providers have been receptive to and interested in our findings, specifically showing interest in decreased missed opportunities for vaccination, increasing the number of patients offered the vaccine, and developing strategies to remind patients to complete the vaccine series.

**CPRIT Grantee Poster Session A**

**Increasing HPV vaccination rates in a U.S.-Mexico border community** Amir Hernandez, Texas Tech University Health Science Center at El Paso; J. Molokwu; N. Shokar

Introduction: Tiempo de Vacunar is an evidence-based program which is designed to reduce HPV related cancer rates in a Hispanic, low-socioeconomic area. The program is tailored specifically to the needs of the community and reached individuals without access to care, HPV vaccines, and health navigation services. Eligibility requirements were those between the ages of 9 and 26, who are Texas residents, who have limited or no insurance, and who have not completed the three dose HPV vaccination series. Eligible participants received a pre-education survey which contained questions on their awareness, knowledge, and intentions on HPV and the HPV vaccine. A brief educational session was then given to the participants; afterwards a post-education survey was administered containing the same set of questions as the pre-education survey in order to measure the changes in knowledge, awareness, and intentions. Finally, participants were administered the HPV vaccine at no cost. Navigation services were then offered to the participant to complete the three dose series over the 6 month dose schedule. Finally, a post program survey was given to assess changes in knowledge, awareness, and intentions since the beginning of the program. Results: A total of 458 (31.9%) participants were recruited, 687 of whom were adults and 735 of whom were children. From these, 1190 (83.7%) completed one dose, 679 (47.7%) completed two doses, and 385 (27.1%) completed three doses. A total of 875 (61.5%) participants initiated the series within the study and 315 (22.15%) initiated outside of the study. A total of 454 (31.9%) participants completed the three dose HPV vaccination series. Conclusions: Increasing community awareness and knowledge of HPV vaccine as a means to prevent cervical cancer and providing no-cost vaccine to those who otherwise would not have access to it will impact the community at large by reducing the burden of HPV infection in the community thereby reducing incident cervical cancer in the area.

**CPRIT Grantee Poster Session B**

**Barriers to completion of HPV vaccination series among a mostly Hispanic population in El Paso county** Amir Hernandez, Texas Tech University Health Science Center at El Paso; J. Molokwu; N. Shokar

Introduction: Published studies have identified numerous barriers to vaccination against the Human Papilloma Virus (HPV). Frequently cost is identified as a barrier; other deterrents reported were low knowledge of the HPV vaccine, and lack of credibility. A lack of health care provider recommendation of the HPV vaccine has proven to be an important barrier as well. Methods: Participants were recruited at various events and sites throughout El Paso County by community health workers. Eligibility requirements were those between the ages of 9 and 26, who are Texas residents, who have limited or no insurance, and who have not completed the three dose HPV vaccination series. A brief education session on HPV, the HPV vaccine, and HPV associated cancers was given. Participants were administered the HPV vaccine at no cost. Navigation services provided by the program allowed participants to complete the three dose series over the 6 month dose schedule. Navigation notes were kept to provide a history of each participant’s case. Qualitative data from navigation notes were thematically analyzed. Results: Major barriers to HPV vaccination by participants included difficulty in getting out of work or school. Both young and older participants cited that the HPV vaccine “sounds gross.” Younger participants also recognized the difficulty in scheduling the doses around school. Numerous participants stated that they had moved out of town and could no longer receive the vaccine series with the program. Various young women identified pregnancy as a barrier to vaccination; these women become pregnant after intake. The program does not vaccinate pregnant women or breastfeeding women. Some participants no longer wished to participate in the program due to their desire to complete the vaccine series with their primary care provider. Finally, countless participants could not be reached. Various barriers for this included, no answer and no message on the PDI. Two disconnected, voice mailbox was full, and wrong number. Conclusions: Several actions were made to decrease the barriers to vaccination for participants. Home visits by the program staff was implemented in order to provide services to participants directly to their homes. Additionally, the program staff has worked on weekends and after work hours in order to accommodate the participant’s schedules. A participant who wishes to complete the doses with their principal care provider was encouraged to do so since the program aims to increase HPV vaccine uptake regardless of where they receive the service.

**CPRIT Grantee Poster Session A**

**Perceptions of a faith-based cancer primary prevention program in Hispanic faith communities** Summer Wilmoth, The University of Texas at San Antonio; E. Martinez; L. Carillo; M. Pan; E. Sosa; Z. Yin; D. Parra-Medina; L. Neira; A. Price; M. He

Introduction: The Body and Soul Example (BHT) Program is a translation of the Body and Soul Program in predominately Hispanic church settings in San Antonio, TX. BHT aimed to reduce cancers risks through integrating spiritual and physical health promotion to facilitate lasting healthy lifestyle changes. Methods: BHT was a 4-month multi-component program including Health Ministry Committee (HMC), church environmental and policy changes, health sermons, health Bible study, nutrition education and cooking demonstration, Active Living Competition, and Peer Coaching. BHT was delivered by trained church health lay leaders. Focus groups were conducted to solicit insights about BHT feasibility, facilitators, barriers and impact. Using a semi-structured interview guide, two trained moderators facilitated the discussion. All sessions were audio-taped and transcribed verbatim. Inductive content analysis was performed with strategies e.g., member checking, debriefing, and team-analysis approach to enhance trustworthiness of data interpretation. Results: A total of 10 focus groups with 55 participants were conducted. Most participants were females, Hispanic, over the age of 40, employed or retired, and with some college education. 1. Training and support: Lay leaders perceived they received adequate training, though more refresher and online training were warranted. It was suggested that leaders would benefit from improving all components of the program to enhance the support throughout the program was highly valued. 2. Program delivery: All intervention components were reportedly successfully implemented, except for Peer Coaching, which was only implemented in a few churches in a support group setting. HMC members valued the flexibility of program components, implementation from the top down, support from the program leaders/pastoral/clergy, leading by example, promotion, community partners and external funding were viewed as program facilitators. Perceived barriers are: heavy burden of paperwork, language and culture, a lack of youth institutional support, church leadership and volunteer transition, and loss of motivation over time. 3. Perceived BHT impact: The BHT was viewed as impactful. The faith-health connection was perceived as necessary in health programming in church settings. Program reception varied by church size, with a higher participation and larger impact reported in small to medium sized churches. Many churches reported healthy environment and policy changes throughout the implementation of the program. External funding were optimistic of BHT sustainability through continued HMC and future plans to broaden or re-implement the program. Conclusions: BHT took a holistic approach by integrating and promoting spiritual and physical health to reduce cancer risks. Program participants viewed BHT to be feasible, successful, and sustainable in the faith-communities.

**CPRIT Grantee Poster Session B**

**Current efforts to increase human papillomavirus vaccination rates in Starr County, Rio Grande Valley** Ana Rodriguez, The University of Texas Medical Branch at Galveston; R. Rupp; K. Yong-Fang; S. Kaul; J. Baillargeon; G. Baillargeon; I. Tijerina; C. Martin; K. Schmeler; M. Edgerton; E. Baker; M. Lopez; S. Fisher-Hoch

Introduction: Schools are a trusted institution within the community with access to both parents and children. School-based vaccinations are successful in delivering other vaccines and may increase HPV vaccine access and uptake. For our CPRIT funded project, an environmental scan
was used to develop a school-based HPV vaccination model targeting recommended age groups. This collaboration was between Rio Grande City Consolidated Independent School District (RGCCISD), Starr County Health Department, the University of Texas Health Science Center School of Public Health – Rio Grande Valley, the University of Texas MD Anderson Cancer Center, and the University of Texas Medical Branch.

Methods: We analyzed baseline HPV vaccination rates reported by the RGCCISD and surveyed parents of eligible children aged 9-13 years about HPV. The parent survey included: (1) demographic information; (2) an assessment of parental knowledge about the HPV vaccine; and (3) information about their children and HPV vaccine experience, including reasons for not receiving the HPV vaccine, having children who graduated high school that received the HPV vaccine, and their child’s current enrollment status in the Texas Immunization Registry (ImmTrac). A comparison between baseline HPV vaccination rates of RGCCISD and National Immunization Survey-Teen (NIS-Teen) was made. Descriptive statistics for the parent survey are in progress.

Results: Based on vaccination data reported by RGCCISD, as of 09/01/2016 there were 7,606 students aged ≥ 9 years in RGCCISD, of which 12.2% completed the HPV vaccine. Baseline HPV vaccine completion rates were lower for RGCCISD students aged 12-14 years compared to students aged 9-11 years (6% versus 15%). Among RGCCISD students aged 12-14 years, 30% received 1 dose and 6% received 2 doses. RGCCISD HPV vaccine completion rates were higher among females aged 12-14 years than males (6.5% versus 4.9%). HPV completion rates for RGCCISD adolescent females and males at baseline was substantially lower than those reported in NIS-Teen (National completion rate: 42% versus Texas: 41% and 24% respectively). Conclusions: Baseline HPV vaccination rates in RGCCISD are far below national and state averages and do not meet the Healthy People 2020 goal of 80%. Using results from our environmental scan, we will pilot a school-based vaccination program at 5 additional middle schools in 2018, with the goal of significantly increasing HPV vaccination rates in the region.
access to treatment for the HCV positive patient population. Through the program we anticipate to reach 160,000 community members, screen at least 12,000 in both phases of the study and deliver the intervention to 363 and identify 480 new chronic HCV patients that will be counseled and linked to care. Conclusions: HepVISTA targets system-wide HCV screening and navigation to treatment and therefore prevents HCC. As a result, it will avoid unnecessary costs and high service utilization, reduce readmissions, and improve end-stage liver disease management.

355 CPRIT Grantee Poster Session B

Effectiveness of best practice alert and provider education for hepatitis C screening among baby boomers Mamta Jain, The University of Texas Southwestern Medical Center; B. Adamson; L. Quirk; B. Turner; A. Singal

Introduction: Effective screening and treatment of hepatitis C virus (HCV) among baby boomers, born between 1945-1965, can reduce the incidence of hepatocellular cancer (HCC). We examined the effectiveness of a simple best-practice alert (BPA) within our electronic medical record coupled with provider education to increase HCV screening and linkage rates among baby boomers. Methods: We implemented a BPA in June 2015 coupled with provider education in a large urban safety net health system in Dallas County. We compared baby boomers without prior HCV screening with an outpatient appointment between 6/1/15-5/31/15 -before BPA, to a group of unscreened baby boomers with an outpatient appointment between 6/1/15-8/26/17- after BPA. Comparison of rates for HCV antibody (Ab), HCV RNA, and linkage-to-care (i.e. completing a liver clinic appointment after HCV diagnosis) were performed using generalized estimating equations controlling for gender, ethnicity, insurance status, and clinic. Results: Of 56,727 at-risk baby boomers seen before BPA implementation, 10.3% had HCV screening performed. HCV RNA confirmatory testing was completed in 54.2% of the 1117 HCV Ab-positive patients, and 43.1% (n=201) of patients with confirmed HCV infection (RNA positive) completed a liver clinic appointment. Among the 39,351 baby boomers seen after BPA implementation, the BPA was not acted on by the provider for over half of patients (52.7%). For those patients with response to BPA, providers ordered HCV Ab for 36.3%, and turned the BPA off for 11%, HCV RNA confirmatory testing was performed in 74.7% of the 163 HCV Ab-positive patients and 45.3% of patients with confirmed HCV infection (RNA positive) completed a liver clinic appointment. The intervention including BPA and provider education was associated with significantly increased odds of HCV antibody screening (AOR 5.42; 95%CI 5.22-5.62), confirmatory testing with HCV RNA (AOR 2.38; 95%CI 1.96-2.90); however, the linkage to care rates was not significantly improved (AOR 1.61; 95%CI 0.88-1.54). Conclusions: Implementation of a simple BPA and provider education significantly increased hepatitis C screening; however, linkage to care rates remain inadequate at only 50%. Further study is needed to understand reasons for turning the BPA off as well as interventions to improve linkage to care of patients with HCV infection are needed to reduce HCC burden in Texas.

356 CPRIT Grantee Poster Session A

Development of Provider Training to Increase HPV Vaccination among 11-26 year olds in a Federally Qualified Health Center (FQHC) Lara Savas, The University of Texas Health Science Center at Houston; J. Delaney; I. Valencia-Torres; K. Bundage; T. Megdal; M. Mims; L. Ramondetta; M. Fernandez

Introduction: Multilevel interventions can increase HPV vaccination rates in community health clinics. Legacy Community Health (Legacy), a large Federally Qualified Health Center located in Harris and Jefferson Counties, implemented evidenced-based system level changes and provider education, to increase HPV vaccination initiation and completion rates among eligible patients aged 11 through 26. In 2013, 18.5% of eligible Legacy patients initiated the HPV vaccine and of those, 57% who received the second dose completed the third. Legacy collaborated with the University of Texas Health (UTH) Science Center at Houston and MD Anderson Cancer Center (MDACC) to develop targeted training for Legacy providers to improve provider HPV recommendation and increase HPV vaccination rates. Methods: Intervention Mapping, a systematic approach for developing theory and evidence-based interventions was applied to 1) identify sub-behaviors necessary for providers to deliver strong HPV vaccine recommendations; 2) specify determinants for these behaviors; 3) create matrices of change objectives; 4) select methods and strategies to influence determinants of behaviors; and 5) produce training materials incorporating these methods and strategies. UTHHealth collaborated with MDACC to develop a comprehensive, targeted provider training. Legacy implemented the resulting in-person and Web-based training for pediatric, family medicine, and OB/GYN physicians, medical assistants; nurses; and care team assistants (providers) to improve communication skills regarding HPV vaccine recommendations, as well as reduce missed opportunities for vaccination. Results: An HPV vaccine advocate and gynecological oncologist from MD Anderson will delivered the training to Legacy providers between March and May 2016. In January 2017, training materials were modified to incorporate revised CDC HPV vaccination recommendations and feedback from Legacy providers. For example, Legacy requested the inclusion of HPV vaccination recommendations for specific population groups including people with disabilities, immunocompromised patients, HIV-positive patients, transgender people, and gay or bisexual men. To accommodate busy clinic and provider schedules, the revised training is delivered via webinar. This format offers a more flexible learning environment and reduces disruption to clinical service delivery. Between April and June 2017, 117 Legacy providers completed the Web-based training. Conclusions: Participatory and systematic planning processes were important for developing training components for Legacy providers. Intervention Mapping provided a systematic process for identifying and addressing specific needs, developing key messages and training materials to address them. Using Intervention Mapping facilitated the development of provider training to increase HPV vaccination, which goes beyond typical knowledge based education and enables practitioners to engage in best practice when providing HPV vaccine recommendations.

357 CPRIT Grantee Poster Session B

An innovative social marketing strategy for increasing HPV vaccination Efraf Gabay, The University of Texas Health Science Center at Houston; S. Vernon; D. Santa Maria; C. Healy; J. Wilkerson; M. Aguilar; G. Johnson; S. Misra; R. Atterstrom; K. Eldersveld; R. Addy; P. Guadalupe; N. Slaughter; A. Jervis; D. Pacheco; A. Cuccaro

Introduction: Since the human papillomavirus (HPV) vaccine was introduced in 2006, vaccine-type HPV prevalence decreased 71% among female youth aged 14-19 years. The Advisory Committee on Immunization Practices (ACIP) recommends a 2-dose vaccination schedule for 11- to 14-year-old adolescents, but HPV vaccination rates are below the Healthy People 2020 goal of 80% completion. The goal of this project is to increase HPV vaccine uptake and completion among minority youth in medically underserved areas in Houston, Texas. To increase knowledge, positive attitudes, and intentions regarding the HPV vaccine, as well as vaccine initiation and completion, we are using a 3-prong strategy: 1) A parent-focused social marketing campaign, including culturally-appropriate messages; 2) Comprehensive school-based vaccination clinics (SBVCs) held in public middle schools, at which youth will be offered all ACIP-recommended adolescent vaccinations; and 3) Annual continuing school nursing education. Methods: To develop the social marketing campaign, we conducted an extensive discovery process. Discovery components included audience segmentation of parents of 11-14-year-olds in target schools, review of the relevant literature, in-depth surveys of team members regarding HPV and HPV vaccination, two design sessions, and the intervention, and 11 focus groups with content experts in health communication, cervical cancer screening and treatment, and adolescent medicine. Results: We developed “All for Them”, an innovative social marketing strategy targeting parents of 11-14 year olds. “All for Them” provides parents with the message that to fully protect their child, it is important for parents to make sure that their child gets all of the recommended adolescent vaccinations, including HPV vaccine. Creative collateral illustrates concepts such as “You wouldn’t give your child half an umbrella” and includes the tagline “It’s All for Them, Because All is Better than Some.” Materials in the campaign will include posters at schools prior to the school-based vaccination clinics, a cover letter and fact sheet included with the vaccination clinic consent packets sent home to all parents, a website, and targeted social media ads for parents whose children attend target schools. As we are in the preliminary stages of this project, results are not yet available for presentation. Conclusions: This project can reduce the incidence of vaccine-preventable cancer, future HPV-related cancer morbidity and mortality rates, increase access to immunization services for youth in Houston MUAs, and establish a program of SBVCs in public middle schools that can continue once funding has ended.

358 CPRIT Grantee Poster Session A

Entre Familia: Evidenced-based Services Program Edna Villarreal, The University of Texas at Austin; D. Morales-Campos; L. Crocker; M. Morales; N. Silva; C. Rohr-Allegreni; L. Trevino; A. Lopez; C. Leal; J. Garza; E. Silva.

Introduction: Cervical cancer is the most common HPV-associated cancer among Hispanic women. In Hidalgo County, women experience higher incidence and mortality from cervical cancer compared to the state and nation. Prevention of cervical cancer is possible using the HPV vaccine, which the Advisory Committee on Immunization Practices recommends for males and females ages 11-26 years. Despite this
recommendation, uptake of the HPV vaccine remains low for Hispanics adolescents and young adults in Texas. The Entre Familia (EF) program integrates a community education component (public education and health professional training/education) and clinic component (provider-directed intervention and healthcare systems-based intervention) to increase HPV vaccination initiation and completion rates in Hidalgo County. **Methods:** Community health workers (CHWs) at community and clinic sites engage a sample of Hispanic adults (ages 11-17 years) and young adults (ages 18-26) who have not initiated or completed the vaccine series. As part of the community component of EF, CHWs engage in county-wide outreach activities, delivering group health education sessions using a flipchart and one-on-one sessions with an educational brochure. This component also provides education and training for community-based healthcare providers. The clinic component of EF will educate and train healthcare providers to implement evidence-based strategies to increase vaccination rates and to make strong recommendations for the HPV vaccine to their patients. CHWs will implement healthcare systems-based interventions (e.g., clinic-based patient education and patient reminders) selected by the lead clinical provider at each site to increase vaccination rates. **Results:** The EF program is currently underway. We expect EF to increase HPV immunization rates (initiation and completion) through implementation of clinic and community components in Hidalgo County. From 3/2017 to 5/2017, we: (1) reached 1,157 adult residents of Hidalgo County through outreach; (2) educated 349 adult residents of Hidalgo County using EF’s evidence-based education sessions and brochures; (3) educated 109 healthcare professionals; (4) served 46 vaccine-eligible clinics that the clinic CHWs; and (5) trained 5 (primary care health care providers on evidence-based HPV vaccination practices; (6) increase over baseline the proportion of healthcare providers that routinely offer the HPV vaccine; and (7) meet or exceed Texas’ vaccine initiation (39%/16%) and completion (20%/8%) rates for adolescents and young adults. EF will also use clinic electronic medical records. Patients reported increasing vaccine initiation and completion among adolescents and young adults, EF has the potential to reduce cervical cancer incidence and mortality among Hispanic women in Hidalgo County.

**CPRIT Grantee Poster Session B**

**“Dancing, Not Wrestling”: Promoting Patient Behavior Change By Exemplifying the Change Johanna Becho, Cancer Prevention and Research Institute; W. Calmbach**

**Introduction:** Obesity is a major health care problem for patients in Texas, and is an independent risk factor for several cancers. Designed with obese patients in mind, the South Texas Ambulatory Research Network (STARNet) developed an evidenced-based educational intervention utilizing Motivational Interviewing (a counseling style) to assist STARNet primary care physicians, physician assistants, nurse practitioners, and staff help overweight and obese patients reduce or stabilize their weight. This 8-session intervention bolsters patient understanding of the value of weight loss and detailing coupled with a simple counseling approach, to promote screening and prevention. **Methods:** “Motivational Interviewing” (MI) is patient-centered, counseling style for eliciting behavior change. MI positions patients to resolve ambivalence associated with healthy behavior change, using skills of MI including: (1) Open ended questions, Affirmations, Reflective statements, Summaries (ORS); (2) Agenda Setting; (3) Scaling, and (4) Recognizing Change Talk. Training includes a brief PowerPoint presentation incorporating short videos, 5-minute practice sessions, and group discussion. STARNet clinics participate in 4 Motivational Interviewing training sessions and a “Research 101” (Human Subjects Protection) training, prior to study launch. Participants complete a modified version of the Motivational Interviewing Knowledge and Attitudes Test (MIKAT) to determine content knowledge/retention, and complete session evaluations. Participants are highly encouraged to contact the program without exception between training sessions, share ideas or express concerns through the process. **Results:** To date, we have successfully enrolled 19 clinics. Practice trainings thus far have taught our team new lessons about viewing each clinic as an individual system, each with their own “personality” and each with their own set of strengths and weaknesses, as they contend with competing demands central to busy primary care practices. **Conclusions:** Variables enhancing each clinic’s capacity to adopt Motivational Interviewing and enroll/track 50 patients include: A.) training intervals B.) emphasis on cultural competency training C.) key relationships with health professionals, (C.) collective practice and D.) Diffusing power differentials E.) Cultural considerations, F.) considering “Zip Code” advantages/disadvantages G.) Modeling the “Spirit of MI”. H.) Research as a form of “investing” in clinic staff. This study reveals potential to incite change at the micro level (counseling dynamics) in order to create change on the macro level (population health). Our observations suggest busy primary care practices may benefit from participating research initiatives with potential to reduce obesity rates and foster research appreciation.

**CPRIT Grantee Poster Session B**

**Establishing a clinic-community collaboration to promote HPV vaccination in South Texas Raquel Romero, The University of Texas Health Science Center at San Antonio; D. Parra-Medina; L. Granado; D. Morales-Campios; J. Botello; P. Winkler; J. Bazan; O. Garcia**

**Introduction:** Every year in the US, doctors diagnose an estimated 19,200 women and 11,600 men with a cancer caused by HPV (human papilloma virus) infection. The HPV vaccine offers a potential powerful primary prevention strategy to decrease incidence of HPV-related cancers. Yet, the initiation and series completion rates, particularly among Texas adolescents, remain extremely low. This project aims to decrease the morbidity and mortality associated with HPV-related cancers by increasing HPV vaccination rates among adolescents, ages 11-18 years, through community outreach and education, a Provider Directed Intervention (PDI) and Health Care System (HCS) strategies. **Methods:** This Quality Improvement program targets six clinics from a Federally Qualified Health Center in four medically underserved rural counties (Frio, Medina, LaSalle, and Dimmit). For community outreach and education, two trained outreach coordinators engage in county-wide outreach activities and deliver health education in group sessions using a flipchart or one-on-one with a brochure. They also provide education and training activities to healthcare professionals in the community. For the PDI, a practice facilitator (PF) delivers continuing medical education sessions to health care providers focusing on evidence-based strategies to increase HPV vaccination rates in their practice. The PF also provides training to Clinic Immunization Champions regarding the HCS strategies (e.g., clinic-based patient education, scheduling vaccination appointments, and patient reminders). We used descriptive statistics to summarize process data (e.g., # persons contacted, # education sessions, and # participants educated) and provide preliminary baseline and 6-month follow-up vaccine initiation and completion rates. **Results:** The program is currently ending its second year. We expect the program will increase HPV immunization rates (initiation and completion) through implementation of clinic and community components. From 3/2016 to 5/2017, we (1) reached 18,097 adult residents, (2) educated 3,797 adult residents using evidence-based education sessions and brochures; (3) educated 452 health care providers; (4) 192 adolescents received a vaccine. Baseline data show that 5% of eligible patients receive one or more doses of the HPV vaccine. Conclusions: By increasing awareness and education throughout community events and clinic interactions, we have been seeing a remarkable increase in the number of people that receive HPV vaccine, which offers the benefit of potentially reducing HPV–related cancer and associated diseases.

**CPRIT Grantee Poster Session B**

**Interim Results of a Tiered Patient Recall/Reminder Program for Human Papillomavirus Vaccination in a Safety Net Healthcare Setting 国 Houston, Texas; L. McGee; M. Daheri; H. Sangi; M. Mallory-McRae; L. Hansen; K. Kline; M. Anderson; J. Boom; M. Scheurer; M. Jibaja-Weiss**

**Introduction:** Each year, there are 26,900 cases of human papillomavirus (HPV)-associated cancer in the US. Despite the HPV vaccine’s safety and acceptability, vaccination rates for adolescents remain low. In 2017, we implemented a tiered patient tracking, reminder/recall, and navigation program as part of a multicomponent intervention to improve HPV vaccine initiation and completion rates in a large, urban safety net healthcare system. Here we present interim results from Year 1 of the program. **Methods:** The tiered program involves creating and managing a registry of age-eligible pediatric patients. Patients’ vaccination status is categorized as unvaccinated, partial (1 dose), or complete (2 or 3 doses, according to age-specific guidelines). Patients are prospectively tracked and receive reminder/recalls for doses 2 and 3. Clinics (n=23) were randomly assigned to an “early” (Group 1, G1) or “delayed” (Group 2, G2) for staggered role out. To date, G2 clinics have not received the intervention. Among G1 clinics, implementation is currently focused on 11-12 year olds who have received 1 dose of the vaccine. We assessed clinic-level baseline and Year 1 initiation and completion rates among 11-12 and 13-18 year olds. The Wilcoxon sign rank test was used to compare Baseline versus Year 1 among G1 and G2 clinics. Baseline and Year 1 rates were based on patients whose last visit was between 01/01/15 - 12/31/16 (n =11,581) and 04/01/16 - 04/30/17 (n=7,254), respectively. **Results:** Baseline initiation and completion rates were respectively 58.4% and 32.8% among 11-12 year olds and 74.0% and 52.1% among 13-18 year olds. Year 1 rates were respectively 65.4% and 38.2% among 11-12 year-olds and 76.0% and 56.0% among 13-18 year-olds. Baseline completion rates were lower in G2 versus G1. Increase in initiation rates between baseline and Year 1 was similar among G1 and G2, overall and by age group. Increase in completion rates was statistically significant among 11-12 year olds in G1 (8.6% increase, p =0.02), but not those in G2 (2.7% increase).
increase, p = 0.37). Increase in completion among 13-18 year olds was similar among G1 and G2 clinics. **Conclusions:** Over the assessment period, the intervention program was targeted to 11-12 year olds in G1 clinics. Completion rates significantly improved for 11-12 year-old patients in clinics that received the intervention (G1) while remaining unchanged in clinics that did not (G2). Our results indicate that tiered patient tracking, reminder/recall, and navigation is effective at increasing HPV vaccine completion rates in a safety net healthcare system.

362 **Poster Session A**

**Using best practices to promote HPV vaccination among adolescents in rural health care settings in south Texas**

Laura Crocker; The University of Texas at Austin; R. Romero; C. Rohr-Allegri; E. Villamor; D. Parra-Medina; D. Morales-Campis

**Introduction:** The incidence of cervical cancer in Health Services Region (HSR) 8 (10.5) and 11 (10.6) continue to be the highest in the state, but HPV-immunization rates remain low among Texas adolescents. The most significant indicator for adolescent vaccination is provider recommendation. Therefore, provider education and support staff training is critical. Other barriers to HPV vaccination include infrequent healthcare visits, missed opportunities for vaccination, and lack of health insurance and/or a medical home. **Methods:** We have implemented two HPV-specific Immunization Champions programs in seven rural clinics in HSR8 and four clinics in HSR11 to improve adolescent HPV vaccination rates in these areas. The “champion” is empowered to promote vaccination through improved clinic systems and patient and provider education. Staff conducted chart reviews using the Comprehensive Clinical Assessment Software Application (CoCASA) and collected baseline data for 336 and 100 randomly selected patients between the ages of 11 and 17 in HSR8 and HSR11, respectively. In HSR8, staff trained Champions to communicate with parents, contact patients overdue for their HPV vaccine to schedule an appointment, and prompt providers to offer the vaccine to eligible patients in the clinic, thereby avoiding a missed opportunity. In HSR11, staff will begin similar efforts upon completion of the needs assessment. **Results:** In HSR8, 15 patients (4.46%) had initiated the HPV series with at least one dose. Of these, just one eligible patient (0.30%) had completed the three dose series. Three patients (0.89%) had received two doses and 11 patients (3.27%) had received only one dose. After six months, HPV-vaccine initiation nearly doubled to 29 (8.61%). Three patients (0.89%) completed the series, while nine patients (2.67%) received the 2nd dose. Missed opportunities dropped from 7.74% at the start of the project to 2.08%. In HSR11, 40% of eligible 11-17 year olds had completed the appropriate HPV vaccine series at the start of the study, with 28 missed opportunities. Follow-up data will be available during subsequent stages of the project. **Conclusions:** The efforts of the Immunization Champions have led to an increased uptake of the HPV vaccine in the clinics in HSR8 through reminder/recall and avoiding missed opportunities. We expect to see a similar improvement in HPV vaccination rates in the HSR11 clinics.

363 **Poster Session B**

**Be Well Communities: A place-based approach to cancer prevention and control**

Ruth Rechis, The University of Texas M.D. Anderson Cancer Center; A. Brewster; E. Caballero; K. Oestman

**Introduction:** A broad range of scientific evidence indicates that more than 50% of cancers can be prevented by focusing on areas such as diet, physical activity, preventive care, UV radiation, and tobacco control. A critical step is to identify and implement the most effective means of putting this knowledge into action in the community. This presentation will highlight how a cancer center, in partnership with a corporate partner, developed and implemented a community action plan for a place-based approach to cancer prevention and control. **Methods:** After receiving significant support from ExxonMobil, a rigorous process was followed to develop a place-based approach for implementation and to create an enabling environment for implementation. Specifically, interviews, a literature review and program assessments were conducted both to identify components of Healthy Community approaches that could be applied to cancer and to identify scientifically-supported interventions which would be relevant in a cancer prevention and control context. Baytown, Texas was selected for this project (population: ~76,000) based on a community assessment and proximity to the corporate partners’ location. The community assessment was conducted to understand the current state of health, strengths of the community, areas of need and to identify key stakeholders for a Steering Committee. The Steering Committee (SC) was led through a consensus process to prioritize scientifically-supported strategies from those that had been identified. Based on the chosen strategies, interventions were modified based on the needs and capacity of the community. The SC organizations submitted work plans which were organized into a comprehensive community action plan. **Results:** Five components of successful approaches for implementing a Healthy Community which could be applied to cancer were identified. A database of approximately 100 strategies focused on cancer prevention and control was developed. The Steering Committee, the funder and the lead institution approved the community action plan and subsequently funding was allocated to the collaborating organizations to carry out the interventions. MD Anderson Cancer Center will continue to serve as the backbone organization to support the work and provide cancer prevention expertise. In Baytown, 9 organizations will carry out 17 interventions focused on diet and physical activity initially and will address additional high impact areas over time. **Conclusions:** Modeled on several decades of Health Community approaches, this initiative has successfully yielded a place-based resident-driven, cancer prevention community action plan to be implemented over the next five years. Using this place-based approach, cancer centers and similar health systems could have a significant impact on addressing cancer prevention and control by engaging the community.
It was hypothesized that patients living in Smith County would be more likely to follow-up and receive a colonoscopy after a positive FIT, and that this follow-up would occur sooner than for patients living outside of Smith County. Results: Between positive FIT and colonoscopy, patients living in Smith County were 2.22 times more likely to follow-up and receive a colonoscopy after a positive FIT, B = .80, p = .015. Patients received a colonoscopy 14 weeks after a positive FIT, and that this follow-up would occur sooner than for patients living outside of Smith County, are warranted in order to have a truly successful rural outreach program. Conclusions: Cada Paso del Camino offers a unique partnership model that could be used to inform similar future efforts within and beyond Texas’s Rio Grande Valley.
up, including colonoscopy with biopsy and LEEP, are being performed by a board certified gynecologist. Results: The program team has provided co-testing: follow-up colonoscopy with biopsy and/or LEEP to 57 women. Of those undergoing follow-up, 28 have been diagnosed and treated for dysplasia, while two have been diagnosed with cancer, one squamous cell and the other adenocarcinoma. The program continues to grow with support from the outreach team. Meetings have been held with 7 providers, resulting in 36 contracts across the rural service area for the provision of clinical services for eligible clients. Conclusions: Moncrief Cancer Institute is addressing access barriers to improve cervical cancer screening participation among rural and medically underserved women across North Texas through its comprehensive program. Training nurses to elevate their scope of practice within the confines of their license. Moncrief is able to increase provider capacity within the region, reducing disparities in care.

CPRIT Grantee Poster Session A

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<td>Results from a large mailed outreach program to promote colorectal cancer screening within a safety-net health system</td>
<td>Stacie Miller, The University of Texas Southwestern Medical Center Moncrief Cancer Institute; E. Berry; S. Gupta; M. Koch; F. Irving; H. Pozos; R. Mercado; A. Rodriguez; B. Balasubramanian; K. Argenbright</td>
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**Introduction:** Colorectal cancer (CRC) screening rates are suboptimal among underserved populations such as the uninsured and minorities. While mailed outreach offering non-invasive tests like the fecal immunochemical tests (FIT) has been shown to increase one time screening rates, several challenges remain, including ensuring diagnostic colonoscopy after a normal FIT, and repeat testing after abnormal FIT. Here we report outcomes of a large mailed FIT outreach program, inviting 15,017 individuals to complete at least one FIT over a 3-year period. **Methods:** Uninsured individuals, age 50 to 64, not up to date with screening from a large safety-net health system were selected for mailed FIT outreach conducted over a 3-year period. Outreach included mailed invitation in English and Spanish with an enclosed FIT, and automated and “live” telephone reminders to complete screening. Patients with normal FIT results were re-invited annually, those with abnormal tests were navigated to complete no-cost colonoscopy, and those not responding were not offered further testing. In this analysis, we report the proportion completing: a) FIT after first invitation; b) repeat FIT after 1st FIT with normal results; c) repeat FIT after 2nd FIT with normal results; d) diagnostic colonoscopy after abnormal FIT. In addition, we report the number of patients diagnosed with CRC, advanced adenoma, or non-advanced adenoma. **Results:** Over 3 years, a diverse group of 15,017 individuals received > 1 FIT invitation. Return rates increased from initial to first-re-invitation and again for second re-invitation. Of those with abnormal FIT, 54.0% completed diagnostic colonoscopy. Patients diagnosed with CRC, advanced adenoma, or non-advanced adenoma were 11, 110, and 296, respectively. **Conclusions:** The FIT outreach program has resulted in increased screening rates, several challenges remain, including ensuring diagnostic colonoscopy after a normal FIT, and repeat testing after abnormal FIT. As the program continues to grow both in volume and geography, targeted outreach specific to provider recruitment has enabled the study team to navigate patients to geographically convenient clinical services and as a result improve colonoscopy completion rates. The next step is to analyze metrics collected as part of colonoscopy documentation to evaluate quality across the service area.

CPRIT Grantee Poster Session B

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<td>Colorectal Cancer Screening and Patient Navigation Coalition: Colonoscopy Capacity in a Rural Service Area</td>
<td>Furien Deng, Light and Salt Association; H. Sun</td>
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**Introduction:** There are a total of 386,342 Asian Americans (AAs) living in the Houston and Austin areas (49% of AA in Texas) and cancer is the leading cause of death among AA populations in the US and Texas. With the funding from CPRIT (2015-2018), this project targets Chinese, Vietnamese, Korean and Filipino communities, which have large foreign-born populations with higher rates of illiteracy and experience greater cultural barriers to accessing health care. Lack of coordinated efforts and resource shared among local AA community-based organizations further contribute to these gaps. Thus, this project establishes culturally and linguistically cancer prevention and support programs within each AA community to effectively reduce service gaps and disparities in diagnoses and death among AA populations. **Methods:** The proposed project is a joint effort of 12 AA community-based organizations, clinics and universities targeting Vietnamese, Chinese, Filipino and Korean communities in the Houston and Austin areas. Its four major components include: prevention/education screening services; navigation services; and capacity building. The cancer prevention and screening components address colon, breast, cervical and liver cancer, and healthy eating. Methods of service delivery include: seminars, workshops, health fairs, newspaper articles, and TV programs, one-on-one education, and curriculum-based nutrition classes. The project will include many screenings and HPV tests. The survivorship program provides group-based interventions, patient navigation, and one-on-one support for cancer patients and the capacity building component develops a network to strengthen the capacities of local AA community organizations that address cancer disparities. **Results:** The project is a 3-year project. By the end of the project, it is expected that 77,786 AAs will be educated about breast, colorectal, cervical, and liver cancer prevention; risk factors; the importance of screening and early detection; and healthy lifestyle behaviors. An additional 600 individuals will attend curriculum-based education classes and 90% of AAs will receive screenings. At least 430 cancer patients and survivors will receive support services including navigation services, transportation and language assistance, and psychological consultations. After 1.5 years of implementation, the outcomes have met the larger goals of screening primarily colorectal cancer and hepatitis B. **Conclusions:** Through coordinated efforts, resource sharing, staff and volunteer training, and using various culturally- and linguistically-appropriate outreach mechanisms, the project will significantly enhance AA communities’ capacities to address cancer disparities and reach their targeted populations and generate more behavioral changes within AA communities. Lessons learned and challenges faced by AA communities will also be discussed.

CPRIT Grantee Poster Session C

The El Paso & Hudspeth County Breast Cancer Education, Screening and Navigation Program (BEST) | Navirkiran Shokar, Texas Tech University Health Science Center at El Paso; C. Martin; A. Alomari; R. Salaria; A. Ayyappan; A. Dwivedi; T. Byrd |

**Introduction:** The El Paso & Hudspeth County Breast Cancer Education, Screening and Navigation Program (BEST) has been held with 26 providers resulting in 3,071 patients through the initiatives to participate in CRC screening. Approximately 13% of patients have completed screening at initial invitation, but this rate increases to 45% at annual re-invitation. More than 6% of patients (n=425) have had positive FIT results, requiring diagnostic colonoscopy. Nearly 40% (n=163) have already completed colonoscopy; precancers have been identified in 45 patients, and another eight patients have been diagnosed with CRC. Colonoscopy providers have been identified in 18 of the 21 counties, and include gastroenterologists (45.8%), general surgeons (25%), and family practice endoscopists (29.2%). With increased colonoscopy capacity through coalition growth, the colonoscopy completion rate is expected to improve further. **Conclusions:** Colonoscopy capacity is fundamental to the success of the large scale implementation of CRC screening through organized outreach. As the program continues to grow both in volume and geography, targeted outreach specific to provider recruitment has enabled the study team to navigate patients to geographically convenient clinical services and as a result improve colonoscopy completion rates. The next step is to analyze metrics collected as part of colonoscopy documentation to evaluate quality across the service area.
CPRIT Grantee Poster Session B
Against Colorectal Cancer in our Neighborhoods 2 (ACCION)
Navkiran Shokar, Texas Tech University Health Science Center at El Paso; T. Byrd; R. Salazar; A. Dwivedi

Introduction: Although colorectal cancer (CRC) screening is universally endorsed, screening rates in the US remain suboptimal, particularly among the poor, the uninsured, recent immigrants and Hispanics. In order to address this disparity, we implemented a bilingual comprehensive, theory-based CRC screening intervention (ACCION) that we previously designed and tested. In this second phase, we added new components based on our prior program experience: Methods: Evidence-based core program components are: 1) Outreach through a community network covering El Paso and Hudspeth County; 2) Bilingual education program delivery by certified community health workers (CHWs) in either video-only, or CHW-only versions; 3) Provision of no-cost fecal immunochemical tests (FIT), colonoscopy, and a fast track referral system; 4) Patient navigation to facilitate testing uptake, address barriers, and facilitate health coverage, diagnosis and treatment. New components include an education/ partial navigation pathway to facilitate screening at each visit, with health education; n=9, a targeted screening and expansion to new target areas through direct service provision in new target areas, through support of new CPRIT funded programs and through wider dissemination strategies. Results: Between March 2015 and July 2017, 6,030 participants were recruited, n=9. So far, overall screening test uptake has been 67.5%, 5,554 were eligible for FITs, and 3,723/5,558 (67.0%) completed the FIT test; the uptake among repeat program screeners was 80.8%. The FIT positive rate was 3.0%; so far 140 have qualified for a screening colonoscopy and 82.9% (116/140) completed their screening colonoscopy; 77.39% (89/115) completed a diagnostic colonoscopy; 71 patients were diagnosed with adenomatous polyps, 4 with colorectal cancer, 1 with anal cancer and 2 with carcinoid tumors. All patients were navigated into treatment. An additional 295 insured participants were provided with education/navigation services to facilitate follow-up with the clinic and 74% (207/295) of those who were followed up so far is 54% (86/160). The program is also currently being implemented in a 19 county largely rural area of West Texas through two new CPRIT funded programs, and program staff are providing implementation support. Conclusions: The ACCION program has been successful and implemented in a 21 county area of West Texas. Data suggests that significant barriers exist even among those with health insurance.

CPRIT Grantee Poster Session A
De Casa En Casa: Preventing Cervical Cancer in El Paso County and Hudspeth County
Navkiran Shokar, Texas Tech University Health Science Center at El Paso; T. Byrd; J. Molokwu; S. Winters; J. Calderon-Mora; R. Salazar; A. Alomari; A. Dwivedi

Introduction: Women on the US-Mexico border have a higher cervical cancer incidence rate, are diagnosed at later stages, and have higher mortality compared to non-Border women in the US. In addition, Hispanic women have almost double the incidence of all race/ethnicities and are twice as likely to die from cervical cancer compared to non-Hispanic women. We identified key barriers to screening through an analysis of local data, key informant interviews and focus groups and have designed a program that addresses the needs of our community. Aims: The project is an evidence-based cervical cancer screening program delivered by certified community health workers (CHWs) in either video-only, or CHW-only versions; 3) Provision of no-cost fecal immunochemical tests (FIT), colonoscopy, and a fast track referral system; 4) Patient navigation to facilitate testing uptake, address barriers, and facilitate health coverage, diagnosis and treatment. New components included an education/partial navigation pathway to facilitate screening at each visit, with health education; n=9, a targeted screening and expansion to new target areas through direct service provision in new target areas, through support of new CPRIT funded programs and through wider dissemination strategies. Results: Between March 2015 and July 2017, 6,030 participants were recruited, n=9. So far, overall screening test uptake has been 67.5%, 5,554 were eligible for FITs, and 3,723/5,558 (67.0%) completed the FIT test; the uptake among repeat program screeners was 80.8%. The FIT positive rate was 3.0%; so far 140 have qualified for a screening colonoscopy and 82.9% (116/140) completed their screening colonoscopy; 77.39% (89/115) completed a diagnostic colonoscopy; 71 patients were diagnosed with adenomatous polyps, 4 with colorectal cancer, 1 with anal cancer and 2 with carcinoid tumors. All patients were navigated into treatment. An additional 295 insured participants were provided with education/navigation services to facilitate follow-up with the clinic and 74% (207/295) of those who were followed up so far is 54% (86/160). The program is also currently being implemented in a 19 county largely rural area of West Texas through two new CPRIT funded programs, and program staff are providing implementation support. Conclusions: The ACCION program has been successful and implemented in a 21 county area of West Texas. Data suggests that significant barriers exist even among those with health insurance.

CPRIT Grantee Poster Session A
A Retrospective Analysis of Breast Cancer Incidence Detected by Expanded Access to Screening in Rural West Texas
Kacci Jacoby, Angelo State University Center for Community Wellness; K. Stewart; L. Ross

Introduction: Access to Breast and Cervical Care for West Texas (ABC4WT) is a CPRIT funded breast and cervical cancer prevention program targeting West Texas. The ABC4WT Project arranged breast cancer screening for more than 2,200 high risk adult female residents of 21 counties between 2012 and 2017. Women had access barriers due to rural residence, and a combination of low household income with inadequate insurance coverage. Hispanic women comprised 59%; 37% were non-Hispanic Whites; 87% were age 40 and over. Methods: Epidemiological studies show female breast cancer incidence rates rapidly increased in correlation with better access to mammography screening in the 1980s (Breast Cancer Facts & Figures, American Cancer Society, 2015-2016, p. 6). This poster updates a similar link between breast cancer incidence and access to mammography in rural West Texas. Mounting evidence that Community Health Workers (CHWs) improve prevention is also supported by detailing effective strategies to remove barriers and increase screening among vulnerable rural women (County Health Rankings and Roadmaps, What Works for Health, Community Health workers, Accessed August 1, 2017: http://www.countyhealthrankings.org/policies/community-health-workers). A retrospective analysis of mammography and breast cancer detection in a 5 year CPRIT supported project documented a high incidence of breast cancer resulting from expanded access to screening in the Concho Valley of West Texas. The retrospective results are combined with TCR, BRFFS, and selected demographic data in assessing the possibility of reducing the future risk pool. Results: It is expected that the retrospective analysis will reveal a substantial increase in incidence rates of breast cancer in a rural population experiencing new access to screening. It is further expected that the assessment of reducing the future risk pool will reveal a need for long-term commitment to eliminating barriers to screening. Effective strategies for CHW intervention to facilitate screening and detection will be identified. Conclusions: The results are expected to identify Obstacles to mammography screening mask incidence rates of breast cancer among vulnerable rural women that are significantly higher than revealed in normal annual epidemiological reporting required by the Texas Health and Safety Code. 2) Future reductions in breast cancer incidence are dependent upon removing obstacles to screening for vulnerable populations in rural areas. 3) Strategies employed by CHWs are effective means of reducing access barriers in rural populations.
required follow up with colposcopy and 92.0% (n=102) were completed. Six cancers were diagnosed. Conclusions: A comprehensive cervical cancer screening program can achieve significant screening uptake rates in a high risk population with historically low screening uptake and has the potential to significantly impact cervical cancer incidence and mortality in this border region.

Impact of Targeted Single Service Events 

Sharon Felts, Texas Tech University Health Science Center at Amarillo; R. Layeequr Rahman; L. Santos; B. Talamanes; T. Baker

Introduction: Texas Panhandle has one of highest rates of cervical cancer in the United States. Public Health Department of Amarillo’s 2013 Community Assessment reported 29.9% women of Potter and Randall counties were out of compliance with cervical cancer screening recommendations. TTUHSC Breast Center of Excellence received CPRIT funds on 9/1/2014 to expand breast cancer outreach, education and services program with a goal of performing 525 cervical cancer screening services by 8/31/2017. On 1/22/16, Access to Breast and Cervical Care for West Texas (ABC2WT) reported 127 Pap smears completed. Methods: An inter-professional team of public, private and community partners met to review data and seek alternative approaches for connecting women with services and increasing Pap smears provided. One program element was “Pap Day” to be scheduled during January’s Cervical Cancer Awareness Month, allowing for focused, targeted traditional and social media linked to cervical cancer Strategic planning tools, such as Six Thinking Hats, Team Task Lists, Marketing Plans and Post Event Evaluations, were used for planning, execution and evaluation of results. The team’s goal - perform 50 Pap smears in 5 exam rooms in 4 hours. Results: Traditional and social media resulted in 202,000 indirect contacts, the week prior to the event, 100 direct contacts with women for ABC2WT eligibility for services, and resulting in 80 pre-scheduled appointments. Sixty women kept appointments for Pap smears. Another 40 women were served as walk-in appointments. Of the 100 seen on Pap Day, 67% were out of compliance with current recommendations, with 19% reporting Pap Day to be the first Pap smear. Ninety percent of the women were scheduled to have Pap smears between 1/25/16 and 3/31/16. At the half-way point of ABC2WT, 54% of goal was accomplished and ABC24WT is on target to exceed program goals. Conclusions: Targeted single service events are highly effective in reaching risk eligible population; this success is attributed to: (1) careful analysis of data and access to resources when current methods are not meeting goals • inter-professional team approach • strategic planning tools such as Six Thinking Hats, Team Task Lists, Marketing Plans and Post Event Evaluations. The initial single service event in 2016 resulted in three similar events in 2017.

Change in breast cancer knowledge is associated with a change in intention to be screened in Mexican-origin women after a breast cancer education intervention

Jennifer Salinas, Texas Tech University Health Science Center at El Paso; T. Byrd; C. Martin; A. Alomar; R. Salazar; A. Dwivedi; N. Shokar

Introduction: Mexican American women have low rates of mammogram screening. The aim of this study was to determine the relationship between breast cancer knowledge and intent to receive a mammogram within six months in a sample of Mexican-origin women living in El Paso, Texas. Methods: A total of 489 uninsured Mexican-origin women 50 to 75 years of age who were assigned to treatment or control had complete data at pre and post intervention. Pre-post analysis was conducted using descriptive statistics and logistic regression to determine if a change in knowledge was associated with a significant change in intent between baseline and follow-up data collection. Results: Participants were 56.7 years of age and spoke primarily Spanish (92.6). The majority of the sample had not had a mammogram in three or more years (51.6%) and 14.6% had never had a mammogram. At baseline, the majority intended to be screened for breast cancer within the next 6 months (93.4%). At post-intervention, nearly half of the intervention group had changed their 6-month intent to be screened for breast cancer from likely to unlikely. The change in intent was strongly associated with a change in knowledge of risk of having a first child by the age of 30 and breast cancer being rare after the age of 70. Conclusions: The intent to be screened for breast cancer in Mexican-origin women may depend on the type of knowledge they have. Change in knowledge may influence perceived risk that contributes to intention to be screened.

Evaluation of a community-based breast and cervical cancer screening program delivered among underserved Hispanic women

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Introduction: Hispanic women in El Paso County have higher breast and cervical cancer mortality rates than women’s rates nationally. The Cancer and Chronic Disease Consortium (CCDC), a Breast and Cervical Cancer Services (BCCSS) program provider, and University of Texas SPH-Houston collaborated to deliver an evidence-based breast and cervical cancer screening education program, Cultivando La Salud, originally developed for Hispanics in rural communities. We adapted CLS to increase screening among low-income women in El Paso County. Results: Cultivando La Salud breast mammography and cervical cancer screening among CCDC BCCS program participants. Evaluation of the adapted CLS program, called Unidas Por Vida Y Salud, will inform future program expansion. Methods: Community Health Workers (CHWs) invited women to participate in the Unidas Por Vida Y Salud program. Eligibility criteria included: Hispanic ethnicity, older than 21 years of age, no mammogram within the last 2 years, no Pap smear in the last 3 years, not currently pregnant, no personal history of breast or cervical cancer, and did not have a hysterectomy. Participants were assigned to intervention and delayed intervention groups. Data collectors administered baseline and 6-month follow-up electronic questionnaires to assess potential covariates: demographic and socioeconomic characteristics, health-care-related factors, knowledge, and psychosocial factors related to screening and cancer. Among women in the intervention group versus delayed intervention (comparison). Results: During the 31-month program period, 5,541 women participated in the program. The evaluation group included 654 participants. Among the 404 women in need of a mammogram, overall 40% completed at mammogram at 6 months follow-up. This indicates that significantly more women completed a mammogram in the intervention group compared with the control group (49.3% vs. 37.7%; p = .019). Among the 544 women in need of a Pap test, 46% completed a Pap screening test; however, no significant Pap screening differences were found between the intervention and control groups. Conclusions: CHWs successfully reached and delivered this evidence-based program to 5,541 women in need of screening, reaching more women than originally planned (n=4,100). This program evaluation establishes effectiveness of the CHW-delivered program for mammography screening among low-income Hispanic women with unmet breast and cervical screening needs. While we found increased Pap screening rates among participants, overall screening rates did not differ significantly by intervention group assignment. Future efforts should focus on strengthening the cervical cancer prevention intervention to increase the effect among vulnerable Hispanic women.

Effects of program scale-up on time to resolution for patients with abnormal mammography screening results

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Introduction: The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) established federal funding for state-administered programs to improve breast cancer screening among underserved women. While patient navigation programs have increased screening outcomes such as diagnostic follow-up of abnormal results and reducing time to resolution (TTR), little is known about the impact of program expansion to large rural areas. Rural-related disparities in breast cancer screening are especially concerning in Texas where, 46% of the 254 counties are rural. Objective: Determine whether TTR varies significantly by (a) service delivery time period [before vs. after expansion], (b) location [original vs. expansion county], and (c) participant characteristics, in a cohort of 2,860 women with abnormal screening results who participated in the community-based Breast Screening and Patient Navigation (BSPAN) program between Oct. 1, 2012 – May 1, 2015. Methods: We calculated the proportions undergoing diagnostic follow-up and resolved within 60 days. We used Kaplan-Meier plots calculated median TTR for each program expansion/service delivery time period and abnormal result type. Cox proportional hazards regressions estimated the effect of service delivery period and patient characteristics on TTR. Wilcoxon Rank Sum tests evaluated a priori whether TTR differs between women who received all services in one county versus transferred among counties for services. Results: Most of the 2,860 women who received an abnormal screening result were uninsured (93%), Hispanic (52%), asymptomatic at intake (73%), and received services in an expansion county (64%). Almost all
Early Detection and Screening

(91%; n=2,599) completed diagnostic follow-up during the study period with a median TTR of 16 days. Across service delivery time periods, TTR was 14-18 days. Overall, 92.9% of those who completed follow-up were resolved within 60 days—well above the NBCCEDP quality metric of 75%. However, follow-up was significantly lower for women with a BI-RAD 3 result (59%). Only a small proportion of women needed to transfer to a different county for resolution (n=293; 12.4%). Median TTR was 28 days among those who transferred versus 26 vs. 16 days; p < .001). Conclusions: BSPAN's outreach and patient navigation screening program maintained timely service delivery during expansion and increased access to high-quality screening services among indigent rural populations. Programs should monitor follow-up among women with BI-RAD 3 results as our data showed much lower completion rates and longer TTR. Policies that add a separate quality metric for BI-RAD 3 outcomes could encourage monitoring.

379

CPRIT Grantee Poster Session B

Colorectal Cancer Prevention in a Minority Population via Personalized Education and Navigation Services

Roberto Villarreal, University Health System; L. Meraz; A. McCracken; D. Pineda; V. Mika

Introduction: In Bexar County, colorectal cancer (CRC) is the third leading cause of cancer death. Incidence and mortality rates over 10 years show that Texas is experiencing a significant decline in CRC rates, except in Hispanics. An estimated 60% of CRC deaths are preventable if everyone over age 50 were routinely screened. Early cancer detection can effectively reduce morbidity and mortality by removing precancerous lesions. Given the disparities that exist for minority populations in cancer morbidity and mortality, it is important to monitor the expanded success of the navigated program to address documented barriers and improve CRC screening rates for Hispanic women as well as men. We aim to motivate, initiate, and sustain health-seeking behavior changes through increasing patient knowledge about CRC and the benefits of preventive care, addressing cultural factors, and reinforcing a relationship of trust with University Health System. Methods: We are using our provider referral system (Access Plus), electronic health records, and patient navigation services to increase the number of first time CRC screenings in low-income, uninsured, Bexar County adults, age 50 and older. This program will overcome cultural, social, and system barriers by providing financial and transportation assistance, as well as bilingual patient navigator (PN) services tailored by gender. During the initial face to face interaction the PN delivers medication for the procedure and relevant CRC prevention information provided by the American Cancer Society and University Health System. The face to face interaction allows the PN to educate on properly preparing for the procedure and gives the patient a familiar face to alleviate anxiety when coming in for the procedure. PNs eliminate the gender specific barriers and provide individual level care. Results: Between January 2016 and May 2017, we reached 1,152 uninsured patients that were provided navigated CRC screenings to 574. Of those that completed screenings, 210 (37%) had polyps and 1 had localized cancer. We provided additional navigation services to 210 insured patients and transportation services to 35 insured patients. Program satisfaction has been high, with 98% indicating that the navigator worked with them to overcome challenges to receive CRC screening. Conclusions: The Colorectal Cancer Prevention Screening Program addresses financial, systemic, cultural, and gender-specific barriers to CRC screening for Hispanic men and women. Our patient navigators have provided invaluable support and assistance to low-income, uninsured patients in need of CRC screenings.

380

CPRIT Grantee Poster Session A

Prevalence and characteristics of colorectal polyps among Texas C-STEP colonoscopy recipients

David McClellan, Texas A&M University System Health Science Center; C. Lichorad; R. Pope; V. Nguyen; J. Bolin

Introduction: The U.S. Preventive Services Task Force recommends that adults age 50-75 be screened for colorectal cancer (CRC) through either fecal occult blood tests, stool DNA tests, or colonoscopies. Colonoscopies are regarded as the gold standard for CRC screening because it allows for visual inspection of the colon, as well as the detection and removal of polyps which have the potential to become cancers. The objective of this study was to determine the prevalence and characteristics of colorectal polyps among persons who received screening colonoscopies through the Texas Cancer Screening and Education Outreach Program (C-STEP) colonoscopy program. Methods: We retrospectively reviewed colonoscopy pathology reports for 895 individuals who received colonoscopies between December 2013 and May 2017 and extracted data of patients with polyp findings. Patients were primarily residents of seven counties comprising the Brazos Valley region of Texas, with 7.8% coming from outside the region. Descriptive statistics were conducted to calculate number, size, type, and location of polyps by age, sex, race, and ethnicity. Results: Of the 895 persons who received one or more colonoscopies over a 42-month period (63.5% female, 36.5% male), 241 had a polyp finding (26.9%). Of these, 49.8% were female, and 45% were male. Men with polyp findings were significantly older on average compared to their female counterparts (mean age: 58 vs. 55.5 years). The highest proportion of those with polyps were between ages 50-59 (38%), followed by 50-59 age group (26.8%), 30.7% of Whites had polyp findings compared to 24.9% of Hispanics, and 22% of Blacks. Majority of the polyps were located in the proximal colon (65%), 35% in the distal colon, and about 5% in multiple locations. Tubular adenomas were the most common polyp finding (59%), followed by sessile (45%) and polyps (9%). On average, polyp size was larger in males (0.46cm) compared to females (0.43cm); about the same size across Whites and Blacks (0.47cm), and smallest among Hispanics (0.44cm). The average polyp size was highest among those below age 50 (0.58cm), but lowest among those aged 50-59 (0.42cm), and increased with increasing age (60-69: 0.43cm; 70-75: 0.46cm). Conclusions: Fewer men received colonoscopies; however, such men were older and constituted a significant proportion of those with polyp findings. Screening recipients younger than age 50 were more likely to have larger polyp sizes, possibly due to their high risk. Contrary to much of the literature, Whites had the highest proportion of polyps detected rather than Blacks.
implemented in earlier CPRIT projects (Texas C-STEP and EPICO), and the ACTION project team revised, updated, and packaged these modules for in-person and online delivery, in English and in Spanish. ACTION CHW Instructors have delivered these modules in person to CHWs in Harlingen, Rio Grande City, Corpus Christi, Tyler, Bryan, Austin, and Houston. The same modules are available online at no charge to CHWs across the state through the ACTION project website. All ACTION modules are approved for continuing education credits by the Texas Department of State Health Services. Additionally, the ACTION project supports other CHW organizations in implementing cancer education and navigation training in their own communities. By providing technical assistance, promoting an affiliation model for CHW instructors and programs, and sharing existing educational resources, the ACTION project builds the capacity of CHW organizations across the state to disseminate Colorectal, Cervical, and Breast Cancer prevention, detection, treatment, and survivorship messages. Results: Throughout July 2017, the ACTION project has directly delivered online training to 740 CHWs, and in-person training to 51 CHW instructors and 237 CHWs. These training modules are also available to CHW instructors and programs to deliver to CHWs in their service areas, expanding the reach of the ACTION project. MOUs and affiliation agreements have been signed with three partner organizations as of July 2017, and the project team is providing technical assistance and support to other organizations across the state as well. Finally, the ACTION website, http://chwaction.tamhsc.edu, contains training modules and toolskits for CHWs, as well as information for CHW organizations about best practices, available resources, and technical assistance. Conclusions: The ACTION CHW training and technical assistance to our combination of in-person and online training, web-based resources, and technical assistance and programmatic support represents a successful model for engaging CHWs and partner organizations in community-based cancer education, navigation, and training across Texas.

383
CPRIT Grantee Poster Session B
Factors associated with navigation failure among medically underserved women screened for cervical cancer Trecilyn Hall, Baylor College of Medicine; J. Monteleague; M. Dahen; L. Hansen; M. Jigba-Weiss; M. Peterson
Introduction: Patient navigation has been widely adopted as a standard of care intervention to improve the uptake of cancer screening and evaluation. However, it remains unclear how best to optimize navigation programs to address the needs of specific at-risk populations. Here, we have utilized our experience with navigating medically underserved residents of Harris County, Texas as a platform for understanding how best patient navigation programs can be organized to improve their impact. The specific goal of this project was to identify factors associated with the ability of a comprehensive real-time patient navigation system developed in collaboration with Harris Health to ameliorate health disparities by reducing the rate of cancer detection and patient navigation failure. Prior to IRB approval, demographics and clinical outcomes were abstracted for all women navigated for abnormal cervical cytology by Harris Health, the nation’s 3rd largest safety net health system, between September 1, 2014 and August 31, 2015. All data elements were abstracted from a proprietary database used by program navigators to ensure appropriate follow up. Navigation failure was defined as >1 missed appointments following enrollment. Chi-squared and Mann-Whitney tests were used to evaluate statistical significance. Results: A total of 3,526 women were diagnosed and navigated for abnormal cervical cytology (>ASCUS) within the defined study window. When compared to successfully navigated patients (n=3,298), women with >1 missed appointment (n=226, 6%) disproportionately self-identified as African-American (44% vs. 22%, p<0.0001) and current tobacco users (30.0% vs. 13%, p<0.0001). They were also more likely to have a public source of external funding for their healthcare (55.9% vs. 34.8%, p<0.0001), and were less likely to be diagnosed with low grade dysplasia. Median time to diagnostic resolution among unsuccessfully navigated women was 166 days (Range: 8-1271), significantly longer than women without missed appointments (75 days; Range: 1-1472, p<0.0001). Median time from referral to diagnosis was also longer (58 days; Range: 0-383 vs. 45 days; Range: 1-513, p<0.01). No differences in age, prior history of dysplasia, distance traveled, or acknowledged exposure to intimate partner violence were observed between successfully and unsuccessfully navigated women. Conclusions: Our result suggests that African-American women are disproportionately vulnerable to navigation failure. If confirmed, potential causes for this disparity should be carefully delineated and addressed as part of CPRIT-supported navigation projects.

384
CPRIT Grantee Poster Session A
Champions for Women’s Healthcare: A Navigator-led Breast Health Program Roberto Villareal, University Health System; L. Meraz; M. Martinez; A. McCracken; V. Mika; E. Carlson
Introduction: Breast cancer is the most commonly diagnosed cancer in women and the second leading cause of cancer deaths in Texas women. Underserved and uninsured women are disproportionately affected by cancer, with higher incidence and mortality rates. Access to mammography services is particularly difficult for uninsured and underinsured Hispanic women, who experience barriers to care such as transportation, financial coverage, fear, cultural concerns, and system issues. The A Su Salud Breast Health Program addressed the need for increased education about breast cancer, the importance of regular screening and early detection, and how to navigate the Health System to obtain a mammogram. Methods: This CPRIT-funded health promotion and clinical services program was comprehensive, community-based, and was primarily appropriate to Hispanic women. Through our program, we have utilized a combination of in-person and online training, web-based resources, and technical assistance and programmatic support to develop a successful model for engaging CHWs and partner organizations in community-based breast cancer education, navigation, and training across Texas. Results: From 2014 to 2016, 3,107 women were scheduled for mammograms and navigated by Patient Navigators. Seventy-eight percent (2,435) completed screenings with 1% (25) dropped out. In addition to those women served through our program, we funded 7,210 mammograms, reducing the financial barrier for many women in our community. Overall, our program provided 9,645 mammograms, with 2,475 (26%) from high risk zip codes. Health promotion outreach and education efforts served 557,700 community members through billboards, brochures, posters, printed reminders, and outreach events. Conclusions: The A Su Salud Breast Health Program improved upon current services by reducing barriers to mammograms, improving screening service coordination and increasing awareness of breast cancer screening and early detection. A system change evaluation was conducted using staff interviews, patient focus groups, and cost-effectiveness. Results indicate that the program was cost-effective, integrated suitably into University Health System, improved the Health System’s ability to serve its patients, and earned high patient satisfaction. It provided champions for underserved minority women to navigate the health system who would otherwise not have had access.

385
CPRIT Grantee Poster Session B
Introduction: The Bridge Breast Network (BBN) is an innovative outreach program providing breast cancer prevention, detection, and survivorship services to underserved areas; 2) increase community partnerships in the Eastern/ Western, and Northeast Texas. Since 2014, BBN has served 28 counties in North Texas, with an emphasis on Dallas County. BBN has provided mammography screenings, diagnostic evaluations, biopsies, breast cancer treatment, survivorship services and clinical referrals for over 5,500 unduplicated women since 2014. Methods: The project plans to: 1) increase mammography screenings using facilities and Mobile Mammography units from Methodist Dallas Medical Center, Harris Methodist Hospital Fort Worth, Hunt Regional Medical Center, and Baylor Scott & White Healthcare to reduce structural and geographical barriers to care by providing free mammography services to women in rural and underserved areas; 2) create a comprehensive dataset for uninsured and underinsured women in Southern counties of North Texas to identify medically underserved population groups in the area; 3) conduct education sessions about breast health awareness and the availability of free mammography services utilizing age, language and culturally appropriate materials; and 4) provide diagnostic care and patient navigation services through treatment for women with abnormal findings. Results: Since 2014, BBN has provided mammograms to 2,400 women per year, on average. Roughly 44% of the malignant cancers diagnosed by BBN were discovered at stage 0 or 1, with 14% right in very early stage. 74% of patients were diagnosed at stage 2, demonstrating that approximately 84% of all malignant cancers found by BBN were discovered at a stage that often requires well treatment to complete. Conclusions: 2014-2017 data demonstrate that Bridge Breast Network is meeting its goals of expanding screening, diagnostic, and survivorship services to uninsured and underinsured women in North Texas counties, as well as increasing the number of minority women who are receiving first-time mammograms. Malignant cancers are being caught early, and the expansion of county reach indicates that BBN is meeting an ever-present community need.
ABSTRACTS
PREVENTION

386  
CPRIT Grantee Poster Session A  
Project REACH (Rural Education and Awareness for Community Health): Experiences and Process Evaluation Outcomes to a Community Screening for Breast and Cervical Cancer Program  
Alison Johnson, Coastal Bend Wellness Foundation; G. Pacheco; H. Werfel  

Introduction: According to the Centers for Disease Control and Prevention (CDC), cervical cancer is the number one cause of cancer death for women in the United States, with proportionally higher incidence among Hispanic women. Similarly, breast cancer is the most common cancer in all women, but the most common cause of cancer death in Hispanic women. The Coastal Bend Wellness Foundation (CBWF) is a community-based, non-profit organization that serves the residents of Corpus Christi and women have participated. CBWF provided a myriad of health-related screenings, outreach, and educational activities throughout the area. The Rural Education and Awareness for Community Health initiative (Project REACH) was launched in December of 2015 with the purpose of delivering evidence-based and culturally tailored education and navigation services for breast and cervical cancer early detection among Hispanic women. The evaluation goals are: 1) to improve the overall performance of the project; 2) to improve the overall design of the project; and 3) to determine the level of effectiveness and impact of the project as a whole. Project REACH is currently in Year 2 of implementation. The aims of this study will be to illustrate the challenges, barriers, and experiences related to the implementation of the program and provide preliminary process outcome data related to the evaluation of the program. Methods: The focus of Project REACH has been in providing outreach services via community presentations, to encourage participation in brief education, and to invite participants as a peer health advocate. Participants were asked to complete a pre and post survey, as well as provide demographic information. Key informant will be scheduled in early fall with Project REACH program coordinators to identify potential barriers, challenges, and experiences learned thus far. A sampling frame will be created to interview program participants to invite them in a focus group session to follow-up with their experiences regarding the intervention and to identify ways to better target the population and improve the early detection messaging. Results: A total of 438 have been outreach and 276 individuals participated in Project REACH and completed both pre and post surveys through July 31, 2017. Less than 11% (n=30) have participated in a previous CBWF program. Conclusions: We hypothesize that this program will be invaluable to the community residents, especially for women in rural areas.

387  
CPRIT Grantee Poster Session B  
Building Bridges Initiative: Results of an Outreach, Education and Cancer Screening Refugee Health Project  
Amy Raines Mileikov, University of North Texas Health Science Center at Fort Worth  

Introduction: Resettled refugees, like many immigrant groups, have been shown to have low cancer screening rates thus increasing the chances for higher cancer incidences and mortality rates. The Building Bridges Initiative (BBI) at the University of North Texas Health Science Center is a Cancer Prevention and Research Institute of Texas (CPRIT) funded program that provides cancer education and screening to refugee women and links them into appropriate health services. The purpose of this poster is to describe the results of the first three years of the BBI intervention on adherence to recommended breast and cervical cancer screenings among enrolled participants at baseline and resulting from the intervention. Methods: Trained bilingual and cultural lay health educators from four refugee communities/regions, (i.e., Bhutanese, Karen, Somali and Central Africa) provide group and individual education to women enrolled in the Building Bridges program in 10 different languages. Data for this analysis comes from baseline and post intervention data. Uptake rate to primary screen, and prevalence of abnormal screens were analyzed among program participants. Results: From September 2014 – May 2017, the lay health educators enrolled 433 refugee women and 115 refugee men participants. Cancer prevention education classes were attended by 502 participants. The uptake rate of screenings was 93% (511/548). The large majority had never been previously screened or were not following recommended guidelines (75% needed a pap exam, 85% needed a mammogram, 70% did not know their hepatitis B status). Of those screened, navigation services were provided for 11 abnormal cervical screenings (n=18 cervical screens completed), 15 abnormal mammograms (n=128 mammograms completed), and 22 positive Hepatitis B screens (n=215 Hepatitis B screens completed). Among 100 age appropriate women, 47 women started the HPV vaccine, and 23 (49%) completed the series. Conclusions: As a result of CPRIT funding, we were able to reach a population of underserved individuals, many who had never received a cancer screening. The lay health worker model, which focuses on natural systems in the community setting, was effective in overcoming many of the system-level, cultural, linguistic and structural barriers that prevent refugees from receiving timely and life-saving cancer screenings.
population is projected to result in a 64% reduction in breast cancer, a 54% reduction in ovarian cancer, and a 37% reduction in colon cancer based on previously published risk models. Challenges included insurance problems, transportation, a lack of time, or an inability to navigate healthcare systems. Conclusions: Developing a genetic navigator to perform long-term follow-up for underserved patients had a largely positive impact on cancer surveillance compliance and projected cancer incidence. Development of a navigator may be important in programs for other programs seeking to enhance the effectiveness of their cancer screening programs.

390  
CPRIT Grantee Poster Session A  
Integrating Cancer Prevention Services into Substance Abuse Treatment Centers  
MarthaFelini, University of North Texas Health Science Center at Fort Worth; I. Oluwatosisin; S. Gupta; A. Prykhodko; K. Ukpa; P. Dokpesi; S. Bakre

Introduction: Women in residential and outpatient substance abuse treatment programs represent a broad range of criminally affected indigent uninsured women and sex workers at high risk of cervical cancer. Using preliminary data collected through a nontraditional partnership with law enforcement and over 30 community organizations (Dallas Prostitute Diversion Initiative), we capitalized on an opportunity to create a cancer screening prevention program targeting this population that is more likely to not be adhering to recommended cervical screening guidelines.

Methods: Focus groups conducted among the target population informed the development of an evidence-based and trauma sensitive cancer prevention education that was subsequently integrated into Nexus Recovery treatment for female substance users in Dallas, Texas, and Salvation Army. Cervical screenings were provided at PRISM Health of North Texas which specializes in providing trauma-informed medical care to poor and vulnerable populations. Other screenings provided included anal, breast, HIV / sexually transmitted infections, and hepatitis. A follow-up clinic visit was provided 7 days from the initial screening as a second opportunity to continue prevention messaging, explain screen findings, and navigate abnormalities to diagnostic care.

Results: We served 3278 uninsured women residing across 119 Texas counties while attending residential treatment for substance use disorders in Dallas. A total of 5974 women (including repeaters) attended trauma sensitive cancer prevention classes, where knowledge scores improved 40%. The uptake rate of cervical cancer screenings was 97%, nearly double the rate reported in similar populations (54%). Nine out of ten women participated in all four screenings offered, of which 40% were not compliant with pap screening guidelines. Twelve percent of cervical screens were abnormal, as were 7% of anal screens, and 13% of hepatitis screens. A total of 6067 HIV and STD screens were funded by alternate sources and HIV+ screening guidelines included structural barriers, immediate needs (housing, medical care to poor and vulnerable populations. Other screenings provided included anal, breast, HIV / sexually transmitted infections, and hepatitis. A follow-up clinic visit was provided 7 days from the initial screening as a second opportunity to continue prevention messaging, explain screen findings, and navigate abnormalities to diagnostic care.

Conclusions: Junedetection and screening for breast and colon cancer through a competency-based framework for training primary care providers and physicians-in-training. Judith Livingston, The University of Texas Health Science Center at San Antonio; L. Mette; M. Thomas; C. Aguilar; B. Pollock; J. Tysinger; G. Tomlinson

Introduction: With the increasing integration of genetics/genomics into healthcare, there is a growing need to ensure primary care health professionals (PCPs) can competently deliver genetic services. Yet, medical education programs have had limited success in educating physicians. Recent studies indicate that PCPs continue to have low levels of genetic testing-related knowledge, uncertainty about testing, and inadequate patient communications skills. The situation is more pronounced in South Texas where there is a large underserved population, few genetic resources, and a dearth of PCPs prepared to provide appropriate genetic services. To address these challenges, GRACIAS Texas (Genetic Risk Assessment for Cancer In All South Texas) focused on preparing PCPs, physicians-in-training, and faculty educators to facilitate early detection of breast and colon cancer in high-risk persons unaware of their risks and options for genetic testing and cancer screening. The goals were to assess the educational needs and increase the numbers of PCPs in South Texas trained in early detection and intervention for breast and colon cancer. Methods: The prevalence of knowledge of cancer genetic risk and screening was evaluated using a 25-item instrument to assess educational needs and guide curriculum implementation. We structured the curriculum using the Accreditation Council for Graduate Medical Education (ACGME) core competencies for graduate medical education. Interventions included face-to-face learning and improvement, interpersonal and communications skills, systems-based practice, and professionalism, tailored to cancer genetics. Training was implemented through interactive, small group teaching using clinical vignettes developed with questions aligned to the core competencies and integrated into the expert-led discussion.

Results: Data from the baseline knowledge assessment confirmed the need for cancer genetics education. In a sample of 113 PCPs assessed, 30% were unable to recognize the inheritance pattern of autosomal dominant, 66% answered incorrectly to a question of whether a breast cancer patient was BRCA1 or BRCA2 and 91% responded incorrectly to the question of when to begin breast cancer surveillance in a 19-year-old female with a BRCA2 mutation. During the project period, March 2012–February 2016, direct education to address learning needs was provided to 250 PCPs. Conclusions: All ACGME core competencies for graduate medical education were accomplished and familiar to graduate medical educators and increasingly to practitioners, provided a useful conceptual framework for cancer genetics education and may help residency program directors evaluate their trainees. Implementing the GRACIAS Texas curriculum strengthened cancer genetics service in South Texas. The curriculum is transferable to other settings to help address PCP cancer genetics educational needs.
ABSTRACTS

PREVENTION

Introduction: Chronic hepatitis C virus (HCV) infection is the leading cause of hepatocellular carcinoma (HCC). In the U.S., HCV has the fastest increasing rate of all cancer diagnoses with 3.88% increasing mortality rate from HCC in the nation. The risk of HCC is substantially greater for persons with HCV-related advanced fibrosis or cirrhosis. National guidelines recommend screening adults born from 1945-65 (baby boomers or BBs) for HCV because treatment with direct-acting, antiviral agents can reduce risks of HCC and liver-related mortality. With CPRIT funding, universal BB HCV testing was implemented in 31 primary care practices serving low-income patients in north and south Texas. We examined risk factors for advanced fibrosis/cirrhosis among BBs diagnosed with chronic HCV in this program. Methods: From 5/1/2015 to 08/26/2017, never-tested BBs were screened for anti-HCV antibody and, if positive, tested for HCV RNA. To assess disease severity in BBs with chronic HCV (RNA+), the FIB-4 index was calculated from age, alanine aminotransferase, aspartate aminotransferase, and platelet count. The dependent variable was a FIB-4 >3.25, indicative of advanced fibrosis/cirrhosis. Predictors included: demographics, body mass index (BMI), alcohol abuse/depression, diabetes mellitus (DM), and insurance status. A series of logistic regression models were estimated and results reported from a reduced model which shows similar associations to a full model. Results: Of 1,273 anti-HCV positive BBs, 968 (76.0%) were tested for HCV RNA. Of these, 700 (72.3%) BBs were RNA+ and 608 (86.9%) had FIB-4 data. These 608 subjects characterized by: mean age 58.3 (SD 4.7); 66% men; 56% Black; 27% non-Hispanic White [NHW]; 14% Hispanic; and 31% obese (BMI >30). DM was diagnosed in 31% of BBs and was more common among BBs who tested RNA+. In Texas, 31% of BBs tested exposed to HCV and 17 included an anti-HCV antibody; uninsured (63%). Overall, 139 (22.9%) had FIB-4 >3.25. Adjusted odds ratios (AORs) for FIB-4 >3.25 were: age per year (1.05, 95% CI 1.00-1.10, P<0.033); Hispanic (1.92, 95% CI 1.08-3.40, P=0.026) and NHW (1.38, 95% CI 0.84-2.26, P=0.20) vs. Black; and alcohol abuse/dependence (2.30, 95% CI 1.22, P<0.01), were associated (P<0.001). Conclusions: In this BB universal HCV screening program, 23% had a high FIB-4 >3.25, indicating higher risk for HCC due to advanced fibrosis or cirrhosis. A high FIB-4 was nearly two-fold more likely for Hispanics versus Blacks. Older persons and persons with a history of alcohol dependence were also at increased risk of advanced fibrosis/cirrhosis.

394 CPRIT Grantee Poster Session A Reducing Racial/Ethnic Disparities in Colorectal Cancer Screening: A Comprehensive EMR-Based Patient Navigation Program Including Technology-Driven Colorectal Cancer Outreach and Education Program Ajeesh Sunny, Baylor College of Medicine; L. Rustveld; S. Nash; V. Varghese; J. Salemi; L. Hanser

Introduction: The main objective of this analysis is to present key findings for the time period August 2016 through May, 2017 of a CPRIT-funded project. The project was born out of the need to improve efficiency for navigating and coordinating timely completion of Colorectal Cancer (CRC) screening at two major medical institutions (Baylor College of Medicine and Harris Health System) in Harris county, Texas. The approach taken by this project involves: 1) A CRC screening registry in the Electronic Medical Record (EMR) that captures age-eligible and appropriate (Mean age, 53.9 ± 6.3 years) patients targeted for navigation; 2) An EMR-based patient navigation workbench that includes capturing CRC screening data, outcomes of patient navigation; 3) An interactive CRC education App featuring a standardized colonoscopy preparation guide, modifiable CRC risk factors, and links to existing resources. Methods: Structured Query Language (SQL) program extracted pertinent medical record data (soo-demographics including zip code and county data, CRC screening information, FIT and colonoscopy orders, FIT results, scheduled colonoscopies, Boston Bowel Preparation Scale scores), which was subsequently populated in the EMR patient navigator workbench. This workbench included pertinent variables necessary for patient navigation including documentation and tracking of telephone encounters, and outcome of navigation (CRC screening referrals, scheduled and completed colonoscopies, cancellations, reschedulings, and non-response). The principal intervention during the initial phone call to the patient was discussion of the colonoscopy preparation guide, reviewing details about ingesting the preparation solution, dietary and medication restrictions, and what to do on the day of the procedure. Results: Calls made to patients resulted in 1) 20% of phone encounters occurred as reminder calls, reminder diets instructions, instructions for taking the prep solution, and answering questions that arose. So far, a total of 5,559 age-appropriate (Mean age, 53.9 ± 6.3 years) patients received navigation services (30.4% White, 26.2% Black, 29.1% Hispanic, 7.6% Asian, and 7% Other race). Out of the navigated patients, 4,402 went on to complete CRC screening tests (2,668 colonoscopies, 1,450 FITs, and 84 sigmoidoscopies). Conclusions: Results suggest that the EMR-based patient navigation program is having a positive impact on overall CRC screening completion and a significant impact on timely follow-up of those at high risk for CRC (FIT positive, iron deficiency anemia, and rectal bleeding). The multi-faceted approach taken with the current project provides large scale follow-up and individualized patient navigation services that are sensitive to their needs and more likely to result in successful completion of CRC screening.

395 CPRIT Grantee Poster Session B Universal baby boomer HCV screening a safety net health care system: Who is at risk of HCV infection? Barbara Turner, The University of Texas Health Science Center at San Antonio; A. Singal; T. Melhado; L. Quirk; B. Adamson; J. Sanders; L. Tenner; M. Jain

Introduction: Screening and linkage to care for hepatitis C virus (HCV) infection can prevent advanced liver disease and hepatocellular carcinoma (HCC). Persons born 1945-65 (baby boomers, BBs) comprise 76% of persons with HCV nationally and are recommended for one-time HCV screening by national guidelines. Yet rates of BB screening in the U.S remain low. With CPRIT funding, an infrastructure for BB screening in primary care practices serving low-income patients offers a valuable model for HCV screening implementation. Methods: Starting in 6/1/15, HCV screening and linkage to care in 12 primary care practices in a Dallas safety-net system included: electronic medical record modification; clinician/staff education; patient education; referral to specialty care; disease staging; and treating of chronic HCV. HCV screening metrics tracked include: % of briefly BBs tested for anti-HCV; % anti-HCV positive (+); % tested for HCV RNA (chronic HCV); and % RNA+. In logistic regression models, we examined associations with anti-HCV+ and RNA+ (among HCV+). Predictors include: demographics; body mass index (BMI); diabetes (DM); alcohol abuse/dependence; insurance status. Results: Of 35,940 eligible BBs, 14,164 (40.4%) were tested for anti-HCV and 1,205 (8.5%) were positive. RNA testing in 1,023 (85.0%) of anti-HCV+ BBs identified 632 as RNA+ (61.8% of RNA tested; 45.6% of all screened). Adjusted odds ratios (AORs) for anti-HCV+ were higher (P<0.001) for men (2.04, 95%CI 1.80-2.32) and alcohol abusers (2.07, 95%CI 1.70-2.50) but lower (all P<0.02) for: Hispanics (0.23, 95%CI 0.19-0.28) vs non-Hispanic whites (NHWs); Medicare (0.44, 95%CI 0.35-0.56), private insurance (0.24, 95%CI 0.17-0.36), and uninsured (0.61, 95%CI 0.51-0.73) vs. Medicaid; BMI >30 (0.53, 95%CI 0.32-0.90) vs <25; and those with diabetes (0.66, 95%CI 0.53-0.78). AORs for RNA+ (among HCV+) were higher (P<0.05) for: Black (2.25, 95%CI 1.68-3.02); alcohol abusers (1.57, 95% CI 1.02-2.42) and Blacks (2.01, 95%CI 0.14-2.88) vs NHWs but lower (all P<0.05) for: Hispanics (vs NHW); Medicare or private insurance (vs Medicaid); BMI <30-34 (vs <25). Conclusions: This program screened 40% of eligible BBs for HCV, far higher than nationally. Of screened BBs, 8.5% were anti-HCV+ and 4.5% had chronic HCV (RNA+); both rates over twice those nationally. Men and alcohol abusers were significantly more likely to test anti-HCV+ and Blacks more likely to test RNA+ than NHWs. Hispanics were less likely to test anti-HCV+ or RNA+ than NHWs. Medicaid enrollees were more likely to have chronic HCV, but restrictive eligibility limits access to HCV treatment and effectiveness of HCC prevention efforts.

396 CPRIT Grantee Poster Session A The Effect of A Multifaceted Colorectal Cancer Patient Navigation Program on Quality of Colonoscopy Preparation Luis Rustveld, Baylor College of Medicine; A. Sunny; S. Nash; M. Horsfield; J. Salemi; V. Varghese; L. Hanser

Introduction: The effect of patient navigation on completion of CRC screening has been evaluated in both community- and hospital based interventions, and has been incorporated in our literature. The overwhelming evidence from these studies indicate a positive impact of patient navigation programs on CRC screening completion. However, little is known whether patient navigation improves quality of colonoscopy. The main objective of this analysis is to present preliminary findings on quality of colonoscopy for a CRC CPRIT-funded project at Baylor College of Medicine. Methods: Intervention group included adults aged 50-75, who completed a colonoscopy between August 2016 and May 2017, and who had completed Boston Bowel Preparation Scale (BBPS) data recorded in the Electronic Medical Record (EMR). All patient navigation encounters were captured in a comprehensive patient navigation module with real time CRC screening registry and Graphical User Interface (GUI) embedded in the EMR as a reporting workbench. Directly from this GUI patient navigators viewed and documented all patient navigation outcomes such as telephone encounters (scheduled, canceled, completed and rescheduled) for CRC screening. Intervention patients received colonoscopy preparation education, and reminder calls. The usual care group consisted of patients who completed colonoscopies a year prior to start of the project, and who received standard CRC care, but no dedicated navigation services. Continuous variables

PREVENTION ABSTRACTS
were summarized by means and standard deviations, and statistically significant differences determined by the Student’s t-test, and Analysis of Variance (ANOVA). Results: Analysis of 240 colonoscopy and 435 intervention patients. Significant differences were observed in mean BBPS between intervention and usual care patients (mean BBPS 8.0 ± 1.45 vs. 7.6 ± 1.5, respectively, p = 0.03). Significant intervention impact was evident as well across racial ethnic groups. Mean BBPS scores for African American; reflective of Hispanic testing. Case management; and health navigation services were significantly higher compared to usual care (Blacks: Intervention BBPS 8.0 ± 1.6 vs. Usual Care BBPS 7.5 ± 1.5, p = 0.03; Hispanic: Intervention BBPS 8.2 ± 1.2 vs. Usual Care 7.5 ± 1.2, p = 0.01). No significant intervention impact on mean BBPS scores were observed for Whites and Other racial/ethnic groups. Conclusions: These preliminary findings suggest the EMR-based patient navigation program significantly improved quality of completed colonoscopies compared to usual care. As the project continues to fully implement its patient navigation program in the coming years, analysis of its effectiveness in improving quality of colonoscopies will be evaluated further.

397

CPRIT Grantee Poster Session B

Hepatocellular carcinoma prevention in the high-risk region of South Texas through baby boomer screening for hepatitis C and linkage to care. Trish Methode, The University of Texas Science Center at San Antonio; R. Bobadilla; L. Tenner; M. Jain; A. Singal; J. Guerrero; B. Turner

Introduction: Texas has the highest age-adjusted incidence of hepatocellular carcinoma (HCC) in the U.S. One-time screening of baby boomers (BBs, born 1945-65) has been endorsed by the US Preventive Services Task Force to prevent HCC and liver disease. Over half of incident HCC cases in Texas are in South Texas (S TX) where most residents are Hispanic and many uninsured. Because treatment of hepatitis C infection (HCV) reduces the risk of HCC, S TX is a priority location for novel approaches to implement HCV screening and linkage to care. Methods: From 6/1/2016-5/31/2017, a program for HCV screening and treatment was operationalized in 19 primary care practices within 4 S TX clinic systems. The program includes: electronic medical record (EMR) modification; clinician/staff training; patient education; coverage of testing for uninsured; early intervention for HCV+; and telehealth specialty support for onsite direct-acting antiviral (DAA) therapy. We compare results of anti-HCV screening and RNA testing for chronic HCV across the 4 systems. Results: The highest performing clinic system had 1,103 eligible BBs and tested 575 (52%) while the lowest had 1,894 eligible BBs and tested 447 (24%). Across the 4 clinic systems, mean monthly eligible BBs ranged from 18 to 158 and mean monthly BBs with anti-HCV testing ranged from 13 to 48. Anti-HCV+ rates for screened BBs ranged from 6% to 19%. Across all 4 systems, 80% of anti-HCV+ BBs received follow-up RNA testing. Of all 1,462 RNA tested BBs, 91 (6%) were RNA+, ranging 3% to 9% by system. Of the 91 BBs with chronic HCV, 68 (75.0%) were uninsured and eligible for telehealth specialty support for onsite anti-HCV treatment in the primary care practice. Among these 68 BB, the mean age was 57 (SD=3.9), 44 (65%) were men and 36 (57%) Hispanic. As of 8/31/17, 12 BBs completed onsite DAA therapy, 14 are on treatment, 13 have had telehealth review, and 23 are being staged for review. Conclusions: In 4 S TX clinic systems serving low income patients, 24% to 52% of eligible HCV BBs were screened for HCV, far higher than the reported national rate (13%). The yield of screening has been high, with 6% of all screened patients diagnosed with chronic HCV. With telehealth specialty support, 26 uninsured BBs have been or are being treated for HCV by the primary care practice and 42 are in various stages of gaining access to treatment.

398

CPRIT Grantee Poster Session B

Evaluation of a comprehensive intervention to improve cervical cancer screening and diagnostic follow-up in a safety-net healthcare system. Jane Monteleague, Baylor College of Medicine; P. Alfred; M. Suarez; L. Hansen; M. Dahen; R. Cheria; B. Mushe; L. Scott; M. Jibaja-Weiss

Introduction: Cervical cancer (CRC) screening rates among eligible adults in the U.S. are far below the national 2018 goal of 80%. This is especially true of medically underserved populations. We implemented a multimodal intervention to address low screening and diagnostic follow-up in a high-volume, urban safety-net healthcare system. Here we evaluate the program’s impact on CRC patient care and diagnostic outcomes. Methods: Harris Health System (HHS) is the safety-net healthcare system for Harris County, Texas, which has one of the highest levels of un- and under-insured in the nation. Over the period of analysis (2010 to 2015), a 3-collection Fecal Immunochromatographic Test (FIT) was used to screen average-risk, age-eligible patients (males and females age ≥ 50 years). Colonoscopy was used for diagnostic follow-up. Using the Quality in the Continuum of Cancer Care framework, intervention strategies were developed to address system failures related to detection and diagnosis of CRC. The primary interventions were 1) patient education (linguistically- and culturally-targeted videos viewed in primary care exam rooms and a low-literacy FIT kit); and 2) a tiered patient tracking and navigation system to ensure diagnostic follow-up among FIT-positive patients. Screening, diagnostic, and cancer staging outcomes were compared between 2010 and 2015. Results: Between 2010 and 2015, HHS experienced a 2.5-fold increase in the number of age-eligible patients, from 87,941 to 113,023. During this interval, the proportion of age-eligible patients who received a FIT increased from 24% to 59% (p<0.001). The average return rate was 45.3%, Accounting for the return rate, FIT screening coverage increased from 22% to 34% (p<0.001). Loss-to-diagnostic follow-up decreased from 50% to 5% (p<0.001). Compared to 2010, there was a non-statistically significant decrease in stage IV diagnoses in 2015 (prevalence ratio= 0.77, p=0.076) and a significant increase in stage III (PR = 1.37, p=0.029). Conclusions: Implementing patient education and patient navigation interventions may be effective in addressing low CRC screening and follow-up in a high-volume safety-net healthcare system. At HHS, these interventions were associated with a 2.5-fold increase in the distribution of FITs, resulting in a significant increase in FIT screening coverage. Loss-to-diagnostic follow-up also decreased dramatically. Tumor staging data are suggestive of possible stage migration from stage IV to stage III disease, a diagnosis associated with a 6 to 7-fold increase in five-year survival. Further interventions are needed to address the low return of FITs needed to achieve the 2018 goal of 80% screening coverage.

399

CPRIT Grantee Poster Session B

Improving cervical cancer screening and prevention in the Rio Grande Valley through patient education and navigation and increasing provider capacity Ana Rodriguez, The University of Texas Medical Branch at Galveston; M. Lopez; M. Munsell; A. Ogburn; R. Gowen; A. Milbourne; M. Mallory; L. Guerra; P. Toscano; E. Hawk; L. Campos; M. Gasca; L. Valdez; N. Esquivel; J. Morales; N. Burkharter; E. Robles; M. Ponthromoli; E. Marin; C. Perez; K. Doughette; B. Reininger; S. Fisher-Hoch; K. Schlneider; E. Baker; M. Dahen

Introduction: Cervical cancer is a preventable disease; however in low-resource settings, in the US and globally, a higher proportion of women die from cervical cancer due to lack of access to screening and treatment of pre-invasive disease. The Rio Grande Valley (RGV) along the Texas-Mexico border represents such a region where cervical cancer mortality rates are approximately 30% higher than the rest of Texas. The goal of this program is to increase the number of women undergoing cervical cancer screening in the region and to increase provider capacity to manage abnormal results. Methods: This program consists of two complementary interventions. The first is community education and navigation to facilitate access to cervical cancer screening services offered at high-quality cervical cancer screening sites. The second intervention is to increase providers’ clinical capacity to manage abnormal cervical cancer screening tests through hands-on training courses and ongoing telementoring using Project ECHO® (Extension for Community Health Outcomes). ECHO is a well-established telehealth model of care that addresses health care access by connecting rural and underserved areas with medical specialists in lower resource regions, expanding access to specialty medical care for underserved areas using videoconferencing, case-based learning and patient co-management. Our program consists of biweekly one hour videoconferences to discuss management of cervical dysplasia. Results: Since November of 2014, a total of 9,510 women have been educated on cervical cancer prevention, cervical cancer screening and HPV vaccination. In addition, 13,436 women have been screened (Pap and/or HPV), and 1,785 have undergone colposcopy for abnormal results. A total of 346 were treated with LEEP (Loop Electrosurgical Excisional Procedure) for mild or surgery. Nineteen patients have been diagnosed with CIN2/3 and five have been diagnosed with invasive cervical cancer. Five additional local providers have been trained to perform colposcopy, cervical biopsies and/or LEEP. Eighty ECHO telementoring videoconference sessions have been held with a average of 23 participants per session. Conclusions: Our initial experience suggests that improving cervical cancer screening rates and patient outcomes require a multi-pronged approach that includes community outreach and education, patient navigation within existing systems offering these services and training of providers to provide care locally. The outcomes of this program will help support an expansion initiative to deliver similar programs in Laredo and Northeast Texas.

400

CPRIT Grantee Poster Session A

Eliminating Cancer Disparities in Medically Underserved Immigrant and Refugee Populations in Houston Texas Shane Chen, Asian American Health Coalition of Greater Houston (dba Hope Clinic); A. Caracostis; K. Dunn
**Intervention:** The Asian American Health Coalition dba HOPE Clinic has worked diligently in facilitating access to prevention screenings to eliminate cancer disparities in the medically underserved immigrant and refugee community, and for the last 10 years has worked addressing breast, cervical and liver cancer through preventative and early detection initiatives. “Eliminating Cancer Disparities in Medically Underserved Immigrant and Refugee Populations” has targeted Vietnamese nail salon workers in Southwest Houston, as well as foreign born and refugees that may come from elsewhere in the city. Other underserved populations impacted include uninsured and low-income minorities of all races. **Methods:** The main goal of reducing the cancer burden in the medically underserved immigrant and refugee populations of Houston. In order to utilize best practices methods bridging and accessible cancer screenings and prevention services to vulnerable population in a culturally and linguistically appropriate processes to address breast, cervical, colorectal, lung, and liver cancer. Preventive services are closely integrated with primary care so that comprehensive care may be delivered in a community health center setting with patients partnering with their primary care provider and medical support team. In addition, HOPE expanded services to include health nutrition education to address obesity and malnutrition which impact various forms of cancer. **Results:** Within last three years, HOPE Clinic has bridged prevention services to more than unique 7,321 individuals delivering with more than 36,610 cancer prevention encounters that are accessible and timely. Low income and uninsured women are able to receive comprehensive breast and cervical cancer prevention services, whereas 8,706 pap smears and 3,038 breast cancer screenings were provided. In addition, to screening 4,443 for hepatitis B and 4150 for hepatitis C, HOPE Clinic’s implementation of in house viral hepatitis B and C treatment empowered the medically underserved patients to take charge of their health and partner with HOPE providers, so that by controlling and eliminating viral hepatitis B and C, individuals are assured better health and increased optimal futures. **Conclusions:** To reduce barriers for among medically underserved immigrant and refugee populations, HOPE Clinic has strengthened its own capacity to screen, follow up, and address detected abnormalities so that patients receive timely care. HOPE Clinic serves a unique patient population that is usually underserved in large research studies. Collecting cultural, social, and economic data through HOPE’s electronic health record eClinicalWorks has shown to be useful in understanding the needs of this population and possibly impact care.

**402**

**CPRIT Grantee Poster Session A**

**Using Intervention Mapping to Adapt a Breast and Cervical Cancer Education Prevention Program**

**Andrea Siceluff, The University of Texas Health Science Center at Houston; E. Adlparvar; P. Cuccaro; M. Fernandez; L. Savas**

**Introduction:** Hispanic women experience higher cervical cancer incidence rates and are diagnosed with breast cancer at a later stage compared to non-Hispanic whites. We used Intervention Mapping Adapt (IM Adapt) Culturally adapted at Houston’s CHW program, this evidence-based breast cancer prevention education program delivered by community health workers (CHW) to increase mammography and Pap screening. The adapted program aims to increase breast and cervical screening and HPV vaccination uptake among Hispanics in the Houston and Corpus Christi Gulf Coast area. This work describes the implementation of IM Adapt steps 1, 3 and 4 to incorporate theory and evidence to guide adaptation for urban and suburban Hispanic populations. **Methods:** We applied a participatory approach throughout the IM Adapt process. For IM Adapt step 1, we conducted a needs assessment including a literature review and review of evidence from the previous program evaluations to inform our logic models of change for screening and HPV outcomes. In step 3, we planned adaptations by evaluating the fit of the original program with our new population. This included adapting matrices of behavior change, design and cultural adaptions for the target population, and changing the design of the education program implementation. In step 4, we developed program materials using evidence-based activities adapted for the target population and new community setting. **Results:** We developed a logic model of change based on the needs assessment (table). We identified performance objectives for new determinants, particularly related to overcoming access barriers (step 3). To increase self-efficacy, we identified theoretical methods, such as problem solving, skill building, and goal setting with counseling. For step 4, we created new education materials to facilitate group presentations delivered by CHWs. In the Prezi intervention and the flip chart intervention on HPV screening and vaccination, replaced the original one-on-one delivered flip chart and video. We developed a one-on-one coaching call to provide a personalized, goal setting-approach to increase self-efficacy, skills and support to overcome personal barriers, in addition to a brief telephone-based screening/HPV vaccination call to patients who cannot attend in-person education. **Conclusions:** IM adapt provided a systematic process to guide adaptation of a breast and cervical cancer screening education program to include HPV vaccination, and to meet the needs of underserved Hispanic women disconnected from the healthcare system. A strength of this work is the use of the IM adapt approach, leading to a more comprehensive intervention to meet the needs of medically underserved Hispanic women.

**401**

**CPRIT Grantee Poster Session B**

**Health is Happiness – A breast and cervical cancer prevention program targeting Vietnamese nail salon workers**

**Frances Nguyen, The University of Texas Health Science Center at Houston; V. Schick; T. T. Fernando; Le-Quyen Esquer**

**Introduction:** Vietnamese women have the highest cervical cancer rate in the United States (43.0/100,000) and the lowest rate of Pap test receipt among ethnic/ racial groups in Houston, Texas (47.9%). Additionally, breast cancer is the third leading cause of cancer death among Vietnamese women nationally, and Vietnamese women had the lowest rate of mammography among ethnic/ ethnic groups in Houston (58.4%). Among Vietnamese women, nail salon workers’ (NSW) cancer risk is amplified by work-related barriers that increase their difficulty in getting cancer screening. The purpose of the Health is Happiness (HiH) program was to promote breast and cervical cancer screening among NSW employed by local establishments in Houston. **Methods:** Nail salon establishments in the Chinatown neighborhood of Houston were recruited into the HiH program. NSW at these establishments were approached by a community outreach team consisting of interviewers and lay health educators. NSW were consented, interviewed, and educated prior to being offered culturally appropriate cancer screening navigation services for breast and cervical cancer screening. A second educational session was conducted prior to the post-test interview conducted three months later. **Results:** Of 276 NSW observed at sixty-two participating salons, 187 NSW (67.8%) completed the pre-intervention survey. Sixty-eight NSW (36.6%) were non-compliant with Pap smear guidelines, and thirty-three (25.8%) were non-compliant with mammography guidelines. Of those available for follow-up, 71.2% of NSW had accepted Pap smear navigation and 63.3% had accepted mammography navigation. Four-fifths of the NSW (78.6%) were compliant with Pap and mammography guidelines to 32.9% who did not accept navigation (p=.049). Four-fifths (78.9%) of these women were compliant with mammography guidelines at follow-up compared to 27.3% who did not accept navigation (p<.005). **Conclusions:** Results indicate that NSW participating in a program tailored to their cultural and work needs are motivated to get cervical cancer screening successfully. Community based programs have the potential to reduce underutilization of cancer screening among Vietnamese women in need of these services.
Early Detection and Screening

404 CPRIT Grantee Poster Session A

Innovations in Cancer Prevention and Research Conference

V Lewis Foxhall, The University of Texas MD Anderson Cancer Center; R. Kingston; E. Furlan; R. Blake

Introduction: Colorectal cancer (CRC), the second leading cause of cancer deaths in the United States and the State of Texas, is curable if detected in its early stages, but often fatal when diagnosed later. Studies have shown that CRC screening (CRCS) for the detection and treatment of early cancer, along with medical interventions, is effective in reducing CRC incidence and mortality. According to the Agency for Healthcare Research and Quality (AHRQ), only half of all adults aged 50-75 have ever received age-appropriate CRCS, and in minority populations, that number drops to 30%. The project utilizes an evidence-based approach to increase CRCS through theory-driven frameworks that changes that engage primary care clinicians to discuss the importance of CRCS with patients. Practices are encouraged to pair CRCS with the annual flu shot, an approach with demonstrated effectiveness (Fit FlU) as a Research Tested Intervention Program (RTIP). Our goal is to increase adherence to CRCS recommendations in CPRIT’s priority populations served through primary care clinics, thus reducing colorectal incidence and mortality disparities.

Methods: We have implemented the Alliance for Colorectal Cancer (ACT) Testing, a CRCS coalition involving MD Anderson and community clinics serving the RPA priority populations. The coalition supports the delivery of a program offering take-home fecal immunochemical tests (FTU) to CRCS priority populations in north, east and southeast Texas. These priority populations include, but are not limited to, underinsured and uninsured individuals, those in rural areas, medically uninsured or underserved racial, ethnic, and socioeconomic groups, and those with low screening rates, high incidence rates and high mortality rates.

Results: The project partners with FQHCs and community clinics and has distributed 3999 FTU as of September 2017. The positive rate is 7.4% and all of those patients have received navigation services to colonoscopies, 6 cancers have been diagnosed and all are receiving or have completed treatment.

Conclusions: The program will continue to widen its network of community gastroenterologists to increase the number of positive patients who complete their colonoscopies.

405 CPRIT Grantee Poster Session A

FluFIT on the Frontera project: interim results

Thelma Hurd, The University of Texas Health Science Center at San Antonio; M. Garcia; C. Lozano; R. Rodriguez; S. Sotelo; T. Sunil

Introduction: Colorectal cancer (CRC) screening prevalence is only 30% among Border Hispanics and community specific screening data is lacking. FluFIT on the Frontera, a comprehensive CRC screening program for average risk people, was implemented in Del Rio Texas, a rural/frontier Border community, to increase screening and awareness and characterize CRC screening practices.

Methods: Community and clinic participants received CRC education from trained clinic-based providers and community based promoters from Val Verde Regional Medical Center (VVRMC) and QUAD Counties Promotoras Program, respectively, and were invited to testing and navigation. Demographic, risk factor and screening history were collected. Participants who did not have a primary care provider were assigned to a provider at VVRMC. All test results were given to participants by their assigned/assigned/providers and those requiring colonoscopy were navigated.

Results: In the first 21 months of programming, 286,773 education/awareness encounters were delivered via media, and social networking, and 6810 community members were educated in group/individual settings. A cohort of 4404 adults (1740 males, 40%; 2664 females) aged 50-75 years were evaluated and offered screening. Seventy six percent were Hispanic and 28.6% were uninsured. There were 1699 (39.5%) participants who met average risk screening criteria, an additional 70% were eligible. Within this subgroup, there were 1581 average risk and 1,121 high risk participants. Of these, 1581 average and 635 high risk participants reported prior screening. Among ineligible people, CRC screening prevalence increased from 33.6% in year 1 to 60.2% in year 2. FIT kits were accepted by 1284 (74.3%). The FIT test completion rate among ineligible people was 80% and 77% in the clinic setting.

Conclusions: The FluFIT intervention was successfully implemented and experienced robust male recruitment. The prevalence of CRC screening has increased 1.8 fold over the project period in this cohort and indicates a change in community screening practices. FIT test completion was 2-fold higher among community navigated compared to clinic based screening participants. The unexpectedly elevated proportion of high risk individuals merits broader community wide screening initiatives.

406 CPRIT Grantee Poster Session B


S. de Grubb, Baylor College of Medicine; S. Gonzalez; R. Levine; R. Zoorob

Introduction: Screening with low-dose computed tomography (LDCT) is one tool that may increase the early detection and reduce lung cancer mortality. Most family physicians report discussing US Preventive Services Task Force (USPSTF) screening guidelines with patients at high risk for lung cancer (LC) however, there is a need for further assessment regarding smoking cessation and lung cancer screening practices and services in our clinics.

Methods: A 10- item electronic questionnaire was distributed to members of the Baylor College of Medicine, Department of Family and Community Medicine who provide services in a private practice and community health centers in Houston, Texas, between April-May, 2016. All responses were anonymous and confidential. Descriptive statistics were calculated.

Results: There were 61 respondents within the targeted provider population and the majority were Family Medicine practitioners (70%). Although over 80% of providers asked patients about their smoking behavior and were familiar with the USPSTF LC screening guidelines, less than half had ever referred a patient to a smoking cessation program and only 16% reported having a formal LC screening program in their practice. Most providers discussed the risks/benefits of screening with their patients in some capacity (85%); however, only 42% reported having patients ask if they can or should be screened for lung cancer in the past year. Concerns regarding the implementation of a lung cancer-screening program in their practice included cost, EMR integrated screening tools, referral process, and access to smoking cessation programs.

Conclusions: The findings reflect a likely lack of knowledge about smoking cessation services available to patients and a lack of consistent protocols for engaging in shared decision-making activities with patients who are identified at high risk for LC. Our findings support previous reports that showed gaps in physician knowledge about smoking guidelines and reimbursement, and the need for further educational outreach.
**Poster Session B**

**Effect of colonoscopy outreach versus fecal immunochemical test outreach on colorectal cancer screening completion: A randomized clinical trial**

**Amit Sinali, The University of Texas Southwestern Medical Center; S. Gupta; C. Skinner; C. Ahn; N. Santini; D. Agrawal; C. Mayorga; C. Murphy; J. Tiro; K. McCallister; B.Adamson; W. Bishop; A. Loewen; E. Halm**

**Introduction:** Effectiveness of colorectal cancer (CRC) screening is limited by underuse, particularly in underserved populations. We previously reported a fecal immunochemical test (FIT) outreach program was more effective than colonoscopy outreach and usual care for increasing one-time CRC screening in a racially diverse and socioeconomic disadvantaged cohort of patients; however, long-term effectiveness may be challenged by need for repeat testing and timely follow-up of abnormal results. **Methods:** We conducted a pragmatic randomized clinical trial from March 2013 to July 2016 among 5999 participants aged 50-64 years who were receiving primary care in an urban safety-net health care system and not CRC screen up-to-date. Effectiveness of FIT outreach and colonoscopy outreach increased completion of the screening process (screening initiation and follow-up) during a 3-year period was compared. Patients were randomly assigned to mailed FIT outreach (n=2400), mailed colonoscopy outreach (n=2400), or usual care with clinic-based screening (n=1199). Primary outcome was screening process completion, defined as adherence to all guideline-recommended screening steps: colonoscopy completion, annual testing if normal FIT, diagnostic colonoscopy for abnormal FIT, and/or treatment evaluation if CRC detected. Secondary outcomes included detection of any adenoma and/or advanced neoplasia including CRC. **Results:** All 5999 participants were included in intention-to-treat analyses. Screening process completion was achieved in 38.4% (95% CI 36.4-40.4) of persons randomized to colonoscopy outreach, 28.0% (95% CI 26.2-29.8) receiving FIT outreach, and 10.7% (95% CI 9.1-12.8) receiving usual care. Colonoscopy screening process completion was 27.7% (95% CI 25.1-30.4) and 17.3% (95% CI 15.0-19.7) higher in outreach arms than usual care (p<0.001 for both) and 10.4% (95% CI 7.8-13.1) higher for colonoscopy outreach compared with FIT (p<0.001). Adenomas were detected in 344 (14.3%) colonoscopy outreach, 128 (5.3%) FIT outreach, and 48 (4.0%) usual care participants. Advanced neoplasia was detected in 105 (4.4%) colonoscopy outreach, 49 (2.0%) FIT outreach, and 16 (1.3%) usual care (p<0.001 for both). Adenoma and advanced neoplasia detection was 10.3% (95% CI 9.5-12.1) and 3.1% (95% CI 2.0-4.1) higher for colonoscopy outreach and 1.3% (95% CI -0.1-2.8) and 0.7% higher (95% CI -0.2-1.6) for FIT outreach than usual care (differences between outreach arms: 9.0% (95% CI 7.3-10.7) and 2.4% (95% CI 1.3-3.3), respectively). **Conclusions:** Among persons aged 50-64 receiving primary care at a safety-net institution, mailed outreach invitations offering FIT or colonoscopy, compared with usual care, increased the proportion completing CRC screening process within 3 years. The rate of screening process completion was higher with colonoscopy than FIT outreach.

**Poster Session A**

**Project DERM: skin cancer health education, screening services and outcomes in an underserved population in Harris County, TX**

**Mary Tripp, The University of Texas MD Anderson Cancer Center; Y. Rivera; D. Benson; C. Bernard; S. George; A. Ciurea**

**Introduction:** Five million patients receive treatment for skin cancer annually in the United States. The incidence rate of melanoma has doubled over the past 30 years. In 2017, 87,110 new cases of invasive melanoma are expected. Melanoma incidence is highest in non-Hispanic whites (NHW). Hispanics are more likely than NHW to have thicker melanoma tumors, more advanced stage at diagnosis and higher mortality. Lower socioeconomic status (SES) is associated with thicker melanoma tumors, advanced stage at diagnosis and poorer survival. **Methods:** Project DERM provides skin cancer health education and screening services in underserved, low-SES population. Educational sessions were led by bilingual/ bicultural researchers, audio-recorded and transcribed verbatim. Survey data, includes cervical cancer knowledge, attitudes, beliefs, self-efficacy, health literacy and acculturation. Results: Eleven focus groups and 100 surveys (n= 74 females and n=26 males) have been collected thus far with Hispanic males and females in South Texas. The majority were Mexican-American (50%) and Mexican (35%), the mean age was 51 (SD 13). The majority (93%) of females reported having a Pap smear, however 50% of these same women had not had a Pap smear in 3 years or more, potentially exceeding the recommended interval. In addition, participants did not know if they had HPV co-testing (45%). A majority of participants (55%) reported primarily receiving medical information from the doctor’s office. Focus group narratives were analyzed using thematic content analysis. The preliminary theme from female focus group interviews is: “include males” in cervical cancer prevention education. The overarching theme from male focus group is “closing of cultures” or navigating between scientific knowledge and expected Hispanic cultural norms. **Conclusions:** These results suggest the need for concerted efforts to improve consistent, regular recommended cervical cancer screening and the importance of provider recommendation for cervical cancer screening. Community-based, culturally competent cervical cancer screening intervention strategies including male partners are needed to decrease Hispanic cervical cancer health disparities in Texas.
Prevention

**411**

**CPRIT Grantee Poster Session A**

**Promoting Activity in Cancer Survivors: The PACES program**

**Chad Rethorst, The University of Texas Southwestern Medical Center; C. Skinner; B. Haley; K. Argenbright; M. Trivedi**

**Introduction:** Physical activity is an effective, safe, and evidence-based behavior that improves physical and psychosocial functioning, and potentially improves recurrence and survival among breast cancer survivors. Multiple organizations, including the American Cancer Society, the National Comprehensive Cancer Network, and the American College of Sports Medicine, recommend cancer survivors engage in at least 75 minutes intense or 150 minutes moderate activity per week. Despite the significant benefits of physical activity, at least two-thirds of breast cancer survivors do not meet the recommendations. To encourage breast cancer survivors to increase their physical activity, we developed the PACES program (Promoting Activity through Education and Support) that includes brief physical activity education and self-monitoring, to more intensive lifestyle counseling and on-site supervised activity. However, such interventions are rarely covered by insurance or offered within standard oncologic care, making them out of reach for cancer survivors. In addition, although multiple strategies have proven efficacious, little is known about the optimal intervention strategies for breast cancer survivors.

**Methods:** We aimed to achieve 3 goals: 1) Provide education and evidence-based interventions to increase physical activity among breast cancer survivors treated at the Simmons Cancer Center; 2) Rigorously evaluate changes in physical activity with program staff; and 3) Assess factors related to dissemination and implementation of the PACES program.

**Results:** A pilot trial of the proposed intervention demonstrated feasibility for the program as we observed very good adherence to education sessions (82%) and use of Fitbit devices (90%). Preliminary evidence from the pilot trial indicates increases in physical activity and improvements in psychosocial functioning. We have also conducted focus group work to gather input from survivors prior to program initiation. Survivors identified many motivators for participation in PACES, including opportunity for social support and programs designed specifically for breast cancer survivors. Survivors also expressed interest in a program that supports their efforts to be physically active by providing ‘accountability’ either through self-monitoring tools or frequent contact with program staff.

**Conclusions:** The PACES program is designed to provide physical activity resources to breast cancer survivors and to evaluate the most effective and efficient strategies for increasing physical activity in this population.

**412**

**CPRIT Grantee Poster Session B**

**Active Living After Breast Cancer: Combining physical activity and survivorship navigation to improve quality of life of breast cancer survivors**

**Lizette Rangel, The University of Texas M.D. Anderson Cancer Center; E. Basen-Engquist; E. Skinner; E. Lewis**

**Introduction:** Physical activity is associated with improved quality of life and increased disease-free survivor in breast cancer survivors. Active Living after Breast Cancer (ALABC) is a program funded by the Cancer Prevention and Research Institute of Texas to improve breast cancer survivorship quality of life through increased physical activity and providing survivorship information. The evidence-based program was developed and tested at MD Anderson, and adapted for delivery in the Houston community.

**Methods:** We hypothesized that breast cancer survivors who participate in the ALABC program would show improvements in physical activity, physical functioning, and quality of life. Participants for ALABC were recruited from the Houston community, including a local multi-specialty care provider, the public hospitals, and area support groups. The program was delivered in 12 group sessions. Each session covered behavioral skills for increasing physical activity (40-50 minutes), 10 minutes of physical activity (3-5 minutes of calisthenics and 30 minutes of on-site supervised activity). The program emphasized increasing physical activity through incorporating short bouts of activity throughout the day. At the first and last sessions, participants completed questionnaires (IPAQ, PROMIS Global health short form), performance tasks (6-minute walk, 30-second sit-stand), and anthropometric assessments.

**Results:** The first group began November 2014. Since then we have conducted 34 groups (25 in English, 8 in Spanish and 1 in English/Mandarin). We have screened a total of 489 survivors; 199 have started the program and 132 have completed the program (60% completion rate). Mean age of participants was 59.7 years (SD=10.6, range 34-84). Participants were 51% African-American, 34% white, 9% Asian, 2% other; 24% were Hispanic. Participants report increases in their weekly minutes of walking (p<.000) and moderate to vigorous physical activity (p<.003). Changes in six-minute walk and sit-stand tests improved (p<.000 for both), demonstrating that physical functioning objectively improved. Self-reported quality of life also improved in both the physical health (p<.000) and mental health (p<.000) domains. There were no significant changes in waist circumference or BMI.

**Conclusions:** Data from the ALABC program indicate that the program was effective at increasing physical activity and improving quality of life. Furthermore, it is feasible to deliver to a diverse survivor population, including Spanish-speaking survivors. Participants in the program showed mastery of the program content and indicated they were using the behavioral strategies for increasing physical activity. Future efforts should expand to other cancer survivors and also address disparities among minority cancer survivors.

**413**

**CPRIT Grantee Poster Session A**

**Childhood cancer survivors and parents with regular follow-up have limited understanding of treatments and risks for late effects**

**Jason King, Baylor College of Medicine; P. Lupo; M. Scheurer; M. Gramatges; E. Shohet; M. Fords; M. Horowitz; D. Poplack**

**Introduction:** The Passport For Care Survivor Website (PFCSW) is a patient-centered decision support tool that provides survivors and/or their parents with a cancer treatment summary, an individualized Survivorship Care Plan (in English or Spanish) with recommendations for follow-up screening based on COG LTFU Guidelines, and related educational content.

**Methods:** Childhood cancer survivors in Texas were invited to enroll in the PFCSW during their first clinic visit or after they contacted the PFCSW after being identified through the Texas Cancer Registry. At time of enrollment, survivors and parents were asked to participate in a research study assessing self-reported knowledge of prior cancer history/treatments, potential late effects, and measures they were receiving follow-up care. Results: A total of 343 survivors completed baseline survey (response rate = 35%), including 213 survivors and 315 parents. Nearly 92% reported regular follow up for their cancer diagnosis, 28% of survivors and 24% of parents reported moderate to no knowledge of potential late effects of their cancer therapy. Survivors reported barriers to receiving follow-up care including: busy schedule (27%), poor insurance coverage (17%), perception that follow-up is not needed (8%), and distance to clinic (7%). Parents also reported considerably more fear of being left out of care compared with 20% expressed to be very afraid or extremely afraid, versus 7% of survivors.

**Conclusions:** Our findings stress the importance of distributing a Survivorship Care Plan to childhood cancer survivors, a population who may have an incomplete understanding of the diagnoses and treatments they received as children, and may be unprepared to manage related health risks and needs as adults. Enrollment in the PFCSW has the potential to reduce some of the barriers to receiving follow-up care that were identified in this study by survivors and their parents.

**414**

**CPRIT Grantee Poster Session B**

**Improving Service Delivery to Cancer Survivors in Primary Care Settings**

**Maria Rodriguez, The University of Texas M.D. Anderson Cancer Center; L. Shay; S. Foxhall**

**Introduction:** An estimated 14 million cancer survivors live in the U.S., with up to 18 million expected by 2020. Innovative educational programs to teach primary care providers (PCPs) about the specific needs of long-term cancer survivors are limited. **Methods:** We established a partnership with three Texas family medicine training programs to provide interactive educational sessions focused on survivors’ needs for primary prevention and lifestyle counseling, surveillance and screening, and prevention of psychosocial and long-term effects. In Project ECHO, cancer center faculty and partners led interactive tele-mentoring sessions following a systematic curriculum to share best practices and facilitate case-based problem solving. Surveys assessing resident and PCP knowledge, self-efficacy, and practices regarding survivorship care management were administered through REDCap in July 2016 and 2017. Paired-t tests evaluated differences from baseline to follow-up. Results: Baseline response rates were 64% (60/94) and 59% (55/93) at follow-up. Compared to baseline, providers at follow-up were significantly more likely to report being “very confident” in their knowledge about; appropriate surveillance to detect recurrent breast cancer (5% vs 24%; p=0.01); long-term effects of colon cancer and its treatment (8% vs 18%; p=0.04); potential adverse psychosocial outcomes of colon cancer treatment (24% vs 44%; p<0.01); appropriate screening for new primary breast (29% vs 61%; p<0.001) and colorectal cancers (27% vs 51%; p=0.01); and preventive lifestyle behavioral counseling for breast (39% vs 59%; p=0.03) and colon cancers (37% vs 59%; p=0.01). Participants were also more likely to “strongly agree” they have the skills necessary to: provide follow-up care related to the colon cancer and its treatment (10% vs 28%; p=0.02); initiate appropriate screening for other new primary cancers for breast (28% vs 56%; p=0.01).
and colon cancer survivors (28% vs 58%; p=0.01); and conduct lifestyle/behavioral counseling to prevent cancer for breast (33% vs 53%; p=0.03) and colorectal cancer survivors (34% vs 55%; p=0.02). Finally, providers were more likely to report “always” or “almost always” having a specific discussion with cancer survivors regarding recommendations for future care and surveillance (5% vs 20%; p=0.08). Conclusions: Preliminary results suggest our project has improved provider knowledge, self-efficacy, and practices regarding survivorship care management and delivered the highest levels in areas pertaining to screening and prevention. While significantly improved, knowledge and self-efficacy around surveillance for cancer recurrence remains low. We aim to continue this trajectory of improvement in subsequent project years and disseminate the project to other primary care training sites in Texas and beyond.

415 CRPRIT Grantee Poster Session A

Interactive patient-centered website to prevent dysphagia in irradiated pharyngeal cancer patients

Eileen Shinn, The University of Texas M. D. Anderson Cancer Center; R. Trevino-Whitaker; E. Ramunno; J. McLaughlin; A. Garden

Introduction: While cancer of the throat is highly curable, up to 39% of survivors experience serious permanent swallowing problems. Targeted swallowing exercises performed during radiation have demonstrated efficacy in preventing dysfunction. However, patients find the preventive swallowing exercises to be excessively time-consuming and difficult due to significant side effects from radiation. Methods: During the first two project periods, we have developed a full-scale responsive web-based application program to deliver an effective intervention program to help patients adhere to preventive swallowing exercises and prevent radiation side effects. The website features tracking logs for weight loss, trismus and swallowing exercises, how-to-videos, patient stories and an all-inclusive search bar. The website is also available in Spanish. Patients at Texas Health Care in Fort Worth are receiving the preventive program; due to slower accrual than expected, we have expanded the program to include head and neck cancer patients at UTMB Galveston and at Kelsey Seybold, Houston. All patients will receive 10 weekly behavioral modules with coping strategies, practical side-effect information, and psychological skills training during radiation and during the four post-radiation period. All participants are asked to create a log-in and password, taught how to navigate the program and asked to log in to the website at least once a week during and after radiation. Results: Ninety-four patients have been enrolled onto the prevention program; 52 who received a non-active, pilot version of the web-based program and 42 who have received the full-scale interactive program. Accrual rates are approximately 96%, with the most common reason for refusal is dislike of a computer-based platform. Approximately 52 (38%) of the enrolled patients are either uninsured or low SES patients. Fifteen mobile tablets with monthly data plans have been distributed to patients without access to computers or smartphones. All 92 patients have received preventive and diagnostic speech pathology services, including fiberoptic endoscopic swallowing tests. Of the 42 patients who have been enrolled onto the full-scale interactive website, 75% have logged in at least once over 50% log in regularly throughout the course of their radiation. Patients who have logged into the website have found the program helpful in coping with radiation side effects and helpfulness with adhering to preventive swallowing and trismus exercises. Conclusions: Head and neck cancer patients are willing to use internet-based intervention programs to learn how to cope with radiation and prevent long-term swallowing dysfunction.

416 CRPRIT Grantee Poster Session B

Improving Electronic Documentation of Disease History Among Colorectal Cancer Survivors at UTMB

Christian Alch, The University of Texas Medical Branch at Galveston; P. Lavere; J. Islam

Introduction: Cancer survivors represent a diverse population with a variety of needs in primary care settings. As treatment and management has improved, life expectancy of cancer survivors has increased, leading to a transition of disease-specific follow-up care out of the offices of specialists and into family medicine clinics. Unfortunately, currently no standardized documentation form exists in the UTMB Electronic Medical Record, EPIC. Providers are forced to perform laborious, often futile, searches through the electronic documentation system to obtain data relevant to survivorship care. Methods: The UTMB Epic Database was surveyed for patients with a known diagnosis of breast, colorectal, lung, or prostate cancer. Colorectal cancer survivors were chosen as documentation subjects, with breast, prostate and lung cancer to be updated at a later time. Exclusion criteria included patients no longer receiving care at UTMB and patients exclusively receiving cancer-related care at other facilities. The “social documentation” field of EPIC was filled with the following information for colorectal cancer survivors:

- Cancer type:
- Date of diagnosis:
- Age when diagnosed:
- Pathology report:
- Stage:
- Surgery:
- Surgery Date:
- Radiation:
- Last date of radiation:
- Chemotherapy:
- Completed chemo:
- Last date of chemotherapy:

Chemotherapy agent:
Results: Out of 156 patients identified through the database search, 74 met criteria to be included in intervention. Reasons most often found for not qualifying included death and patients no longer receiving care at UTMB. Full pathologic history (TNM staging) was identified from database review in 88% of male colorectal cancer survivors and 64% of female colorectal cancer survivors. Conclusions: Documentation of cancer survivors can be performed in a primary care settings through meticulous search of EMR records. Further studies can demonstrate how clear documentation of disease history among colorectal cancer patients improves clinical decision making and time restraints in the clinics.

417 CRPRIT Grantee Poster Session A

A Statewide Tele-Mentoring Medical Education Program to Improve Survivorship Care

Maria Rodriguez, The University of Texas M. D. Anderson Cancer Center; G. Palos; L. Foxhall; L. Shay; K. Gilmore; R. Harris; P. Lewis-Patterson

Introduction: Education and guidance on the clinical management of cancer survivors is needed to standardize survivorship care for this growing population. To address this need, a tele-mentoring educational curriculum utilizing Extension for Community Healthcare Outcomes (ECHO) methodology was developed to deliver evidence-based recommended cancer survivorship care and preventive services. Here we present findings from a survey to address satisfaction with the curriculum and program. Methods: The curriculum consisted of hybrid educational sessions provided by the Project ECHO platform. Tele-mentoring video conferencing sessions combined didactic lectures and case studies discussions. Sessions were held twice a month and led by an interdisciplinary team of faculty and providers assigned to clinics of the Survivorship Program of M. D. Anderson Cancer Center. Content focused on the principles and practices of survivorship care, prevention, and management of late effects related to cancer or its treatment. Study investigators developed an evaluation tool to assess: 1) satisfaction with ECHO operations, 2) self-efficacy in clinical management of survivors, and 3) barriers towards distribution of treatment summaries and delivery of survivorship care. REDCap, a secure, web-based application, and was used to develop, distribute and collect data. Results: In June 2017, electronic surveys were distributed to 116 faculty and medical residents in 3 collaborating Texas-based institutions. There was a 46.4% response rate and the majority of respondents attended the ECHO sessions (81.5%). The most common reason for non-attendance related to scheduling conflicts with the ECHO sessions (77.8%). Respondents were split in their ratings of the organization of the clinic, with just over half rating the organization as good or very good (54.5%). Reasons for ratings of fair or poor included: session did not provide information on guidelines, having the learning topics and case studies match and planned the topics in advance, providing handouts with information on where to look for resources on cancer survivorship, have specialist present to answer questions. Almost all respondents reported being interested in continuing participation in ECHO sessions to improve their knowledge and skills (81.9%), and reported that participation in ECHO clinics increased their ability to offer more complete comprehensive care (88.6%). The majority of respondents endorsed the ECHO sessions as an effective way for their clinic to enhance its expertise (77.5%). Conclusions: Overall, participants found the sessions helpful in improving cancer survivors’ care, despite feedback from half reporting there were limitations in the curriculum’s format. Efforts will be made to integrate their suggestions into future program improvements.

418 CRPRIT Grantee Poster Session B

Preserving Hope: Results from the 2017 LIVESTRONG Survey on Fertility Concerns

Kendall Bergman, LIVESTRONG; A. Narayan; C. Bank; K. Treiman; C. Soloe

Introduction: According to the 2009 Behavioral Risk Factor Surveillance Survey, 16% of the more than 24.7 million Texans diagnosed with cancer are under 45 years (reproductive years). Research shows that infertility...
Survivorship affects a cancer survivor’s long-term quality of life by causing unresolved grief and depression, as well as reduced life satisfaction and increased anxiety. Addressing fertility concerns has emerged as a major component of survivorship care. Fertility preservation is often possible in people undergoing cancer treatment. Despite the American Society for Clinical Oncology’s guidelines for oncologists to disclose risks of infertility, health care professionals (HCPs) are not routinely offering fertility information and referrals to their patients. CPRIT awarded LIVESTRONG funds to create a cancer and fertility training to increase awareness of this issue among Texas HCPs, and to increase the number of survivors who receive information about infertility risks and preservation options. Methods: In 2017 LIVESTRONG launched a survey to assess the number of cancer survivors who were informed of infertility risks due to cancer. A total of 123 people diagnosed with cancer between ages of 15-39 during 2006 to 2017 in Texas responded to the survey. Results: Seventy-five percent of respondents reported that a doctor or HCP discussed fertility issues related to cancer treatment with them. Of these respondents, 26% reported that they raised the topic themselves. The majority (76%) reported that they discussed fertility issues with a HCP before starting treatment. Respondents reported that discussion topics included possible risks to fertility (85%), methods for fertility preservation (63%), timing for fertility preservation (43%), and costs of fertility preservation (34%) among other topics related to fertility. However only 40% reported being referred to a fertility specialist. Respondents who did not take steps to preserve their fertility (55%) cited cost, a desire to start treatment right away, and not knowing it was a possibility as reasons for not doing so. Among respondents who did take steps to preserve their fertility (43%), 68% reported receiving financial assistance to cover costs of fertility preservation. Conclusions: Receiving a cancer diagnosis can be overwhelming and cause fear and anxiety. A patient may not be aware of all questions to discuss with a HCP. LIVESTRONG strongly recommends that all HCPs who interact with cancer patients during their reproductive years inform them of any potential risks to their fertility so patients can make informed decisions about taking protective or preservation measures to have hope for a biological family after cancer.
<table>
<thead>
<tr>
<th>Last Name, First Name</th>
<th>Abstract ID</th>
<th>Author Organization</th>
</tr>
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<tbody>
<tr>
<td>Abbara, Sunhy</td>
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<td>The University of Texas Southwestern Medical Center</td>
</tr>
<tr>
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<td>58</td>
<td>The University of Texas Southwestern Medical Center</td>
</tr>
<tr>
<td>Achreja, Abhinav</td>
<td>232</td>
<td>Rice University</td>
</tr>
<tr>
<td>Adair, Antony</td>
<td>252</td>
<td>Rice University</td>
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<td>353, 358, 376, 393, 395, 408</td>
<td>The University of Texas Southwestern Medical Center</td>
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<td>Addy, Robert</td>
<td>357</td>
<td>The University of Texas Health Science Center at Houston</td>
</tr>
<tr>
<td>Adesina, Adekunle</td>
<td>27</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Adiparvar, Emily</td>
<td>402</td>
<td>The University of Texas Health Science Center at Houston</td>
</tr>
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<td>268</td>
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</tr>
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<td>47</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
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<td>245, 276</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
</tr>
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<td>312</td>
<td>Aeglea BioTherapeutics</td>
</tr>
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<tr>
<td>Ahmmed, Md Shamim.</td>
<td>166</td>
<td>Texas Tech University</td>
</tr>
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<td>113</td>
<td>National Cancer Institute</td>
</tr>
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<td>184</td>
<td>Texas A&amp;M University</td>
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</tr>
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<td>398</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
</tr>
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<td>Almasri, Sarah</td>
<td>100</td>
<td>The University of Texas Health Science Center at San Antonio</td>
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<td>Alomari, Adam.</td>
<td>371, 374, 376</td>
<td>Texas Tech University Health Science Center at El Paso</td>
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<td>Aloire, Elizabeth.</td>
<td>178</td>
<td>Baylor College of Medicine</td>
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</table>
Beaton, Graham .............................. 308 .............................................. Curtana Pharmaceuticals, Inc.
Beaver, Josh .............................. 235 .............................................. Texas A&M University System Health Science Center
Becho, Johanna .............................. 359 .............................................. Cancer Prevention and Research Institute
Beck, Jeffrey .............................. 183 .............................................. Organization Not Submitted
Becker, Elisabeth .............................. 211 .............................................. The University of Texas Health Science Center at Houston
Becker, Heather .............................. 224 .............................................. The University of Texas at Austin
Bedford, Mark .............................. 33 .............................................. The University of Texas M.D. Anderson Cancer Center
Bedolla, Roble .............................. 97 .............................................. The University of Texas Health Science Center at San Antonio
Beebe, Kirk .............................. 120 .............................................. Metabolon, Inc.
Behrens, Carmen .............................. 23, 61 .............................................. The University of Texas M.D. Anderson Cancer Center
Bekradda, Mohamed .............................. 318 .............................................. Early Drug Development Group
Benod, Cindy .............................. 32 .............................................. Houston Methodist
Benson, Diane .............................. 409 .............................................. The University of Texas M.D. Anderson Cancer Center
Bensussan, Alena .............................. 177 .............................................. The University of Texas at Austin
Berenson, Abbey .............................. 336, 337, 343, 345 .............................................. The University of Texas Medical Branch at Galveston
Berenson, Emily .............................. 388 .............................................. The University of Texas Southwestern Medical Center
Bergman, Kendall .............................. 418 .............................................. LIVESTRONG
Berisha, Sebastian .............................. 185 .............................................. University of Houston
Bernard, Carolyn .............................. 409 .............................................. The University of Texas M.D. Anderson Cancer Center
Bernard, Vincent .............................. 167, 250 .............................................. The University of Texas M.D. Anderson Cancer Center
Bernini, Juan Carlos .............................. 143 .............................................. Baylor College of Medicine
Bernstam, Elmer .............................. 132 .............................................. The University of Texas Health Science Center at Houston
Berry, Emily .............................. 210, 367, 368, 369 .............................................. The University of Texas Southwestern Medical Center Moncrief Cancer Institute
Bertaina, Alice .............................. 332 .............................................. Organization Not Submitted
Berthiaume, Luc .............................. 328 .............................................. Pacylex Pharmaceuticals Inc.
Bexon, Martin .............................. 322 .............................................. Medicenna Therapeutics, Inc.
Bhattacharya, Pratip .............................. 165, 179, 199, 276 .............................................. The University of Texas M.D. Anderson Cancer Center
Bhattacharya, Suparna .............................. 28 .............................................. The University of Texas M.D. Anderson Cancer Center
Bi, Jiong .............................. 53 .............................................. Baylor College of Medicine
Bills, Gerald .............................. 278 .............................................. The University of Texas Health Science Center at Houston
Bing, Zhang .............................. 25 .............................................. Baylor College of Medicine
Biot, Mathilde .............................. 39 .............................................. The University of Texas M.D. Anderson Cancer Center
Bishop, Wendy .............................. 408 .............................................. The University of Texas Southwestern Medical Center
Bithi, Swastika .............................. 283 .............................................. Texas Tech University
Blake, Rhyon .............................. 404 .............................................. The University of Texas MD Anderson Cancer Center
Blazeck, John .............................. 324 .............................................. The University of Texas at Austin
Blumenschein, George .............................. 319 .............................................. The University of Texas M.D. Anderson Cancer Center
Bobadilla, Raudel .............................. 397 .............................................. The University of Texas Health Science Center at San Antonio
Boci, Federico .............................. 3 .............................................. Rice University
Bohen, Kurt .............................. 130 .............................................. Baylor College of Medicine
Bolin, Jane .............................. 380, 381, 382 .............................................. Texas A&M University System Health Science Center
Bondy, Melissa .............................. 40 .............................................. Baylor College of Medicine
Boom, Julie .............................. 361 .............................................. Texas Childrens Hospital
Borton, Eric .............................. 210 .............................................. The University of Texas Southwestern Medical Center
Botello, Jorge .............................. 360 .............................................. South Texas Rural Health Services, Inc.
Bottiglieri, Teodoro .............................. 175 .............................................. Baylor Research Institute
Bouchard, Richard .............................. 266 .............................................. The University of Texas M.D. Anderson Cancer Center
Bourgogne, Agathe .............................. 319 .............................................. Immatics Biotechnologies
Boyer, Thomas .............................. 36 .............................................. The University of Texas Health Science Center at San Antonio
Bracey, Harrison .............................. 203 .............................................. Texas State University
Braggio, Danielle .............................. 309 .............................................. Beta Cat Pharmaceuticals, LLC
Braun, Frank .............................. 27 .............................................. Baylor College of Medicine
Brenner, Dean .............................. 301 .............................................. Organization Not Submitted
Brenner, Malcolm .............................. 154 .............................................. Texas Childrens Hospital
Bresalier, Robert .............................. 301 .............................................. The University of Texas M.D. Anderson Cancer Center
Brewster, Anna .............................. 363 .............................................. The University of Texas M.D. Anderson Cancer Center
Brogich, Jakoah .............................. 192 .............................................. University of Houston
Bright, Scott .............................. 243 .............................................. The University of Texas M.D. Anderson Cancer Center
Broadus, Russell .............................. 41 .............................................. The University of Texas System
Broniowska, Katarzyna .............................. 120 .............................................. Metabolon, Inc.
Bronk, Lawrence .............................. 269 .............................................. The University of Texas M.D. Anderson Cancer Center
Brown, Alexandra .............................. 81 .............................................. The University of Texas M.D. Anderson Cancer Center
Brown, Veronica .............................. 343 .............................................. The University of Texas Medical Branch at Galveston
Browning, Travis .............................. 214 .............................................. The University of Texas Southwestern Medical Center
<table>
<thead>
<tr>
<th>Name</th>
<th>affiliation and organization</th>
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<td>Fokt, Izabela</td>
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</tr>
<tr>
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<td>The University of Texas at Austin</td>
</tr>
</tbody>
</table>
Gong, Jing ........................................ 189, 421 .............................. The University of Texas Health Science Center at Houston
Gong, Yang ........................................ 201 .................................................. The University of Texas Health Science Center at Houston
Gonugunta, Vijay .................................. 317 ................................................. The University of Texas Health Science Center at San Antonio
Gonzales, Delana .................................. 354 .................................................. University Health System
Gonzalez, Norberto ................................ 364 ................................................................ MHP Salud
Gonzalez, Sandra ................................... 406 .................................................. Baylor College of Medicine
Goodell, Margaret ................................... 74 .................................................. Baylor College of Medicine
Gorfe, Alemayehu ................................... 239 .................................................. The University of Texas Health Science Center at Houston
Gonzonzy, Jorg ...................................... 59 .................................................. Stanford University
Goros, Martin ........................................ 410 .................................................. The University of Texas Health Science Center at San Antonio
Gottesman, Michael ................................. 113 .................................................. National Cancer Institute
Goux, Heather ....................................... 192 .................................................. University of Houston
Gowen, Rose ......................................... 399 .................................................. Organization Not Submitted
Grafanaki, Katerina ................................. 325 .................................................. University of Patras
Gramatges, M. ....................................... 413 .................................................. Texas Childrens Hospital
Granado, Linda ....................................... 360 .................................................. The University of Texas Health Science Center at San Antonio
Grande-Allen, K. Jane ............................... 6 .................................................... Rice University
Grattoni, Alessandro ................................. 107 .................................................. Texas Medical Center
Greenberg, Benjamin ............................... 37 .................................................. The University of Texas Southwestern Medical Center
Grimm, Sandra ....................................... 147 .................................................. Baylor College of Medicine
Grosshans, David .................................... 269 .................................................. The University of Texas M.D. Anderson Cancer Center
Gu, Guo-wei ......................................... 60 .................................................. Baylor College of Medicine
Gu, Jian .............................................. 174 .................................................. The University of Texas M.D. Anderson Cancer Center
Gu, Zhimin .......................................... 22 .................................................. The University of Texas Southwestern Medical Center
Guan, Fada ........................................... 269 .................................................. The University of Texas M.D. Anderson Cancer Center
Guan, Yan ........................................... 119 .................................................. Arizona State University
Guduru, Shiva ....................................... 130, 135, 136, 137 .................................................. Baylor College of Medicine
Guerra, Laura ........................................ 399 .................................................. Organization Not Submitted
Guerrero, Juan ....................................... 393, 397 .................................................. The University of Texas Health Science Center at San Antonio
Guevara, Priscilla .......................... 373 .................................................. Texas Tech University Health Science Center at El Paso
Gui, Xun ............................................. 315 .................................................. The University of Texas Health Science Center at Houston
Guilmette, Amanda ................................. 307 .................................................. The University of Texas M.D. Anderson Cancer Center
Gumbus, Curtis ..................................... 23 .................................................. The University of Texas M.D. Anderson Cancer Center
Gumin, Joy .......................................... 165 .................................................. The University of Texas M.D. Anderson Cancer Center
Gunadi, Sonny ...................................... 212 .................................................. Leeds Institute of Biomedical & Clinical Sciences, University of Leeds
Gundry, Michael .................................... 74 .................................................. Baylor College of Medicine
Guo, Hou-Fu ........................................ 281 .................................................. The University of Texas M.D. Anderson Cancer Center
Guo, Jiaming ........................................ 265 .................................................. University of Houston
Guo, Jing ............................................ 297 .................................................. University of Houston
Guo, Linjie .......................................... 271, 313 .................................................. Baylor College of Medicine
Gupta, Amit ......................................... 239 .................................................. The University of Texas Health Science Center at Houston
Gupta, Sachin Kumar .............................. 4 .................................................. Baylor College of Medicine
Gupta, Samir ........................................ 368, 369, 408 .................................................. The University of California San Diego Health
Gupta, Shuchika .................................... 390 .................................................. University of North Texas Health Science Center at Fort Worth
Gutierrez, Carolina ................................ 63 .................................................. Baylor College of Medicine
Gutierrez-Puente, Yolanda ....................... 333 .................................................. Universidad Autónoma de Nuevo León
Gutscner, Tony ...................................... 232 .................................................. The University of Texas M.D. Anderson Cancer Center
Guzman, Anna ....................................... 74 .................................................. Baylor College of Medicine
Haidar, George ...................................... 241 .................................................. The University of Texas Health Science Center at San Antonio
Hailemichael, Yared ................................ 260 .................................................. The University of Texas M.D. Anderson Cancer Center
Haley, Barbara ...................................... 411 .................................................. The University of Texas Southwestern Medical Center
Hall, Tracilyn ....................................... 383 .................................................. Baylor College of Medicine
Halm, Ethan ......................................... 408 .................................................. The University of Texas Southwestern Medical Center
Haltom, Amanda .................................... 98 .................................................. The University of Texas M.D. Anderson Cancer Center
Hamann, Heidi ..................................... 198, 214 .................................................. The University of Texas Southwestern Medical Center
Hammer, Robert .................................... 58, 72 .................................................. The University of Texas Southwestern Medical Center
Han, Jie .............................................. 8 .................................................. Baylor Research Institute
Han, Leng ............................................ 189 .................................................. The University of Texas Health Science Center at Houston
Han, Richard ....................................... 6 .................................................... Rice University
Han, Ruolan ......................................... 318, 323 .................................................. Saliarius Pharmaceuticals LLC
Han, Yuyan .......................................... 174 .................................................. The University of Texas M.D. Anderson Cancer Center
Hanash, Samir ...................................... 3, 167, 301 .................................................. The University of Texas M.D. Anderson Cancer Center
Hancock, John ...................................... 239 .................................................. The University of Texas Health Science Center at Houston
Hanoteau, Aurelie ................................ 290, 294 .................................................. Baylor College of Medicine

153
<table>
<thead>
<tr>
<th>Name</th>
<th>Page Numbers</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanser, Loretta</td>
<td>361, 383, 394, 396, 398</td>
<td>Harris Health System</td>
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<td>Harlow, Seth</td>
<td>288</td>
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<td>175</td>
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<td>304, 331, 335</td>
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<td>417</td>
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<td>125, 230, 274</td>
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<td>147</td>
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<td>143</td>
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</tr>
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<td>286</td>
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<td>225</td>
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<td>172</td>
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<td>350</td>
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<td>209, 211, 226, 357</td>
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<td>283</td>
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<td>382</td>
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<td>268</td>
<td>Baylor Research Institute</td>
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<td>68</td>
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<td>304, 335</td>
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<td>348, 349</td>
<td>Texas Tech University Health Science Center</td>
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<td>Hernandez, Kristen</td>
<td>377</td>
<td>Cancer and Chronic Disease Consortium</td>
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<td>190</td>
<td>Universidad Autónoma de San Luis Potosi</td>
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<td>23, 61</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
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<td>241</td>
<td>The University of Texas Southwestern Medical Center</td>
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<td>346, 378</td>
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<td>319, 320</td>
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<td>195</td>
<td>University of North Texas</td>
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<td>Hilsenbeck, Susan</td>
<td>63</td>
<td>Baylor College of Medicine</td>
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<tr>
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<td>62, 289</td>
<td>Texas Tech University Health Sciences Center</td>
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<tr>
<td>Hirth, Jacqueline</td>
<td>336, 337, 343, 345</td>
<td>The University of Texas Medical Branch at Galveston</td>
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<td>Ho, Khe-Yu</td>
<td>206, 256, 257</td>
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<td>79, 115</td>
<td>Baylor College of Medicine</td>
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<td>132</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Holland, Benny</td>
<td>381</td>
<td>Texas A&amp;M University System Health Science Center</td>
</tr>
<tr>
<td>Hollingsworth, Neal</td>
<td>184</td>
<td>Texas A&amp;M University</td>
</tr>
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<td>8</td>
<td>Baylor Research Institute</td>
</tr>
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<td>Homan, Kimberly</td>
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<td>276</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
</tr>
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<td>Hooper, Annie</td>
<td>278</td>
<td>Texas State University</td>
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<tr>
<td>Horning, Aaron</td>
<td>146, 277</td>
<td>The University of Texas Health Science Center</td>
</tr>
<tr>
<td>Horowitz, Marc</td>
<td>413</td>
<td>Baylor College of Medicine</td>
</tr>
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<td>Horrigan, Steven</td>
<td>309</td>
<td>Beta Cat Pharmaceuticals, LLC</td>
</tr>
<tr>
<td>Horsfield, Matthew</td>
<td>396</td>
<td>Baylor College of Medicine</td>
</tr>
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<td>288</td>
<td>The University of Texas at Austin</td>
</tr>
<tr>
<td>Horton, John</td>
<td>29</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Hou, Jason</td>
<td>257</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Hrycushko, Brian</td>
<td>262</td>
<td>The University of Texas Southwestern Medical Center</td>
</tr>
<tr>
<td>Hsiao, Hao-Ching</td>
<td>251</td>
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<tr>
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<td>64</td>
<td>Baylor College of Medicine</td>
</tr>
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<td>43</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
</tr>
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<td>199</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
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</tr>
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<td>20</td>
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<td>Hu, Tianyuan</td>
<td>19</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Hu, Yanfen</td>
<td>5, 111</td>
<td>The University of Texas Health Science Center at San Antonio</td>
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<td>112, 290</td>
<td>Baylor College of Medicine</td>
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<td>116</td>
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</tr>
<tr>
<td>Huang, Chung-Huan</td>
<td>184</td>
<td>Texas A&amp;M University</td>
</tr>
<tr>
<td>Huang, Ejin</td>
<td>164</td>
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</tr>
<tr>
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<td>168</td>
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<td>Affiliation</td>
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</tbody>
</table>
Johnson, Gwendolyn ................................................. 357 ................................................. Organization Not Submitted
Johnson, Jane ..................................................... 56, 80 .............................. The University of Texas Southwestern Medical Center
Johnson, Randy .................................................. 18 .............................. The University of Texas M.D. Anderson Cancer Center
Johnson, William ............................................... 142 .............................. The University of Texas at Austin
Johnson-Harris, Carolyn ........................................ 340 .............................. The University of Texas M.D. Anderson Cancer Center
Jolly, Mohit Kumar ............................................... 3 .............................. Tarrant County Challenge
Jones, Philip ...................................................... 32 .............................. Rice University
Jordan, Lee ........................................................... 169 .............................. Texas A&M University System Health Science Center
Jordan, Robert .................................................. 251 .............................. The University of Texas Health Science Center at Houston
Joseph, Bernice ................................................ 366 .............................. The Rose
Jose-Yacaman, Miguel .......................................... 190 .............................. The University of Texas at San Antonio
Jung, Sung .......................................................... 152 .............................. Baylor College of Medicine
Kabat, Christopher ............................................ 247 .............................. The University of Texas Health Science Center at San Antonio
Kabotyaniski, Elena .............................................. 25 .............................. Baylor College of Medicine
Kaghyan, Sahak .................................................. 338 .............................. The University of Texas at San Antonio
Kahen, Elliot ..................................................... 323 .............................. H. Lee Moffitt Cancer Center and Research Institute
Kalainayakan, Sarada Preea ...................................... 21 .............................. The University of Texas at Dallas
Kalhor, Neda ..................................................... 23, 61 .............................. The University of Texas M.D. Anderson Cancer Center
Kalissen, Noah .................................................. 183 .............................. Organization Not Submitted
Kalluri, Raghu ................................................... 98 .............................. The University of Texas M.D. Anderson Cancer Center
Kameoka, Jun ................................................... 298 .............................. Texas A&M University
Kamunyo, Evalyne ............................................... 415 .............................. The University of Texas M.D. Anderson Cancer Center
Kamyabi, Nabillolah .............................................. 34 .............................. The University of Texas M.D. Anderson Cancer Center
Kane, Bob ............................................................ 291 .............................. Baylor University
Kang, Hong ....................................................... 201 .............................. The University of Texas Health Science Center at Houston
Kang, Min .......................................................... 108, 259, 282, 284 .............................. Texas Tech University Health Sciences Center
Kang, Rhea .......................................................... 39 .............................. The University of Texas M.D. Anderson Cancer Center
Kang, Soo ........................................................... 291 .............................. Baylor Scott & White Health
Kang, Tae Hyun ................................................... 267 .............................. The University of Texas at Austin
Kang, Yaan .......................................................... 232 .............................. The University of Texas M.D. Anderson Cancer Center
Kanwal, Fasiha .................................................... 160 .............................. Baylor College of Medicine
Kaoud, Tamer .................................................... 17, 139, 142 .............................. The University of Texas at Austin
Karamitros, Christos ............................................. 324 .............................. The University of Texas at Austin
Kaseb, Ahmed .................................................... 225 .............................. The University of Texas M.D. Anderson Cancer Center
Kasiri, Sahba ........................................................ 96 .............................. The University of Texas Southwestern Medical Center
Katsonis, Panagiotis ............................................. 64, 71 .............................. Baylor College of Medicine
Katz, Matthew .................................................... 167, 250 .............................. The University of Texas M.D. Anderson Cancer Center
Katz, Ruth .......................................................... 177 .............................. The University of Texas M.D. Anderson Cancer Center
Kaul, Sapna ....................................................... 351 .............................. The University of Texas Medical Branch at Galveston
Kaushik, Dharan ................................................ 241 .............................. The University of Texas Health Science Center at San Antonio
Kavvaki, Lydia ................................................... 231, 236 .............................. Rice University
Kebrizaei, Partow ................................................ 319 .............................. The University of Texas M.D. Anderson Cancer Center
Kelenis, Demetra ................................................ 56 .............................. The University of Texas Southwestern Medical Center
Kelvezari, Juili .................................................. 331 .............................. NanoHybrids Inc
Kennedy, John .................................................... 334 .............................. Ion Biotechnology (USA)
Keresztessy, Zsolt ............................................... 334 .............................. Ion Biotechnology (USA)
Kern, William ................................................... 206, 258 .............................. University of Houston
Kerr, Matthew .................................................... 269 .............................. The University of Texas M.D. Anderson Cancer Center
Kerwin, Sean ..................................................... 203 .............................. Texas State University
Kesari, Santosh .................................................. 308 .............................. Organization Not Submitted
Kettner, Nicole ................................................... 272 .............................. The University of Texas M.D. Anderson Cancer Center
Keyel, Michelle ................................................ 279 .............................. Texas Tech University Health Sciences Center
Keyomarsi, Khandan ............................................ 118, 272 .............................. The University of Texas M.D. Anderson Cancer Center
Khairat, Sarah .................................................... 296 .............................. Organization Not Submitted
Khotskaya, Yekaterina ......................................... 132 .............................. The University of Texas M.D. Anderson Cancer Center
Killary, Ann ....................................................... 83, 85 .............................. The University of Texas M.D. Anderson Cancer Center
Kim, Chang ....................................................... 304 .............................. The University of Texas M.D. Anderson Cancer Center
Kim, Dae ............................................................ 94 .............................. The University of Texas Rio Grande Valley
Kim, Dong ....................................................... 167, 250 .............................. The University of Texas M.D. Anderson Cancer Center
Kim, James ......................................................... 88, 96 .............................. The University of Texas Southwestern Medical Center
Kim, Jiha ............................................................. 98 .............................. The University of Texas M.D. Anderson Cancer Center
Kim, Jiyeon ........................................................ 88 .............................. The University of Texas Southwestern Medical Center
Kim, Mihwa ........................................................ 94 .............................. The University of Texas Rio Grande Valley
Kim, Min ............................................................. 128 .............................. The University of Texas Southwestern Medical Center
Kim, Young Won ........................................ 71 .................................. Baylor College of Medicine
Kim, Yu-Ri .................................................. 208 ............................................................... Columbia University Medical Center
Kinchen, Jason ............................................. 120 ............................................................... Metabolon, Inc.
King, Jason .................................................. 413 ............................................................... Baylor College of Medicine
Kingston, Ryan ............................................. 404 ............................................................... The University of Texas M.D. Anderson Cancer Center
Kirby, Neil .................................................... 253, 420 .................................................. The University of Texas Health Science Center at San Antonio
Kriencko, Natasha .......................................... 67 ............................................................... Rice University
Kirma, Nameer ............................................ 134, 151, 277 .................................................. The University of Texas Health Science Center at San Antonio
Kitano, Ayumi ............................................... 19 ............................................................... Baylor College of Medicine
Kline, Kimberly ........................................... 361 ............................................................... The University of Texas at San Antonio
Knowles, Susan ........................................... 308 ............................................................... Curtana Pharmaceuticals, Inc.
Ko, Junho ..................................................... 54 ............................................................... John Peter Smith Hospital
Koch, Mark ................................................... 368, 369 ............................................................... The University of California San Diego Health
Kogiso, Mari ................................................ 27 ............................................................... Baylor College of Medicine
Koire, Amanda ............................................. 64, 71 ............................................................... Baylor College of Medicine
Kok, Melissa ............................................... 225 ............................................................... The University of Texas M.D. Anderson Cancer Center
Koller, David ............................................... 309 ............................................................... Organization Not Submitted
Kollipara, Rahul ........................................... 80 ............................................................... The University of Texas Southwestern Medical Center
Kolonin, Mikhail ......................................... 89 ............................................................... The University of Texas Health Science Center at Houston
Kolosovas-Machuca, Eleazar Samuel ............. 190 ............................................................... Universidad Autónoma de San Luis Potosí
Koneru, Balakrishna ....................................... 62, 284, 289 .................................................. Texas Tech University Health Sciences Center
Kontak, Mark ............................................... 303 ............................................................... VisionSR, Inc.
Kontos, Christos .......................................... 325 ............................................................... University of Athens
Kopetz, Scott .............................................. 229 ............................................................... The University of Texas M.D. Anderson Cancer Center
Korfiati, Aigli ............................................... 325 ............................................................... InSyBio Ltd
Korir, Daniel ............................................... 270 ............................................................... University of North Texas
Kornblau, Steven ......................................... 159 ............................................................... The University of Texas M.D. Anderson Cancer Center
Kornienko, Alexander .................................. 278 ............................................................... Texas State University
Koshy, Sandeep ........................................... 280 ............................................................... Novartis
Kourentzi, Katerina ...................................... 171, 192, 297 .................................................. University of Houston
Krag, Christopher ........................................ 288 ............................................................... University of Vermont
Krag, David ................................................ 288 ............................................................... University of Vermont
Kramer, Jennifer .......................................... 160 ............................................................... Baylor College of Medicine
Kraus, Thomas ............................................ 197 ............................................................... Organization Not Submitted
Kraus, W. Lee ............................................. 2 ............................................................... The University of Texas Southwestern Medical Center
Krishnan, Samaya Rajeshwari ....................... 317 ............................................................... The University of Texas Health Science Center at San Antonio
Krupar, Rosemarie ....................................... 290, 292 ............................................................... Leibniz Center for Medicine and Biosciences
Kuehl, Thomas ........................................... 268 ............................................................... Baylor Scott & White Health
Kulesz, Paulina ........................................... 220 ............................................................... University of Houston
Kum, Hye-Chung ......................................... 191 ............................................................... Texas A&M University System Health Science Center
Kumar, Addanki Pratap ................................. 97 ............................................................... The University of Texas Health Science Center at San Antonio
Kuo, Yong-Fang ......................................... 337, 343, 345 .................................................. The University of Texas Medical Branch at Galveston
Kurenbekova, Lyazat .................................... 99, 114, 326 .................................................. Baylor College of Medicine
Kurie, Jonathan ........................................... 281 ............................................................... The University of Texas M.D. Anderson Cancer Center
Kurley, Sarah ............................................. 63 ............................................................... Baylor College of Medicine
Kuttruff, Sabrina ......................................... 320 ............................................................... Immaicuts Biotechnologies
Kwak, Youn-tae .......................................... 20 ............................................................... The University of Texas Southwestern Medical Center
Kwok, Christopher ...................................... 106 ............................................................... The University of Texas Health Science Center at Houston
Kyburz, Bryce ............................................ 339, 344 ............................................................... Austin Travis County Integral Care
Kyriakopoulos, George ................................ 325 ............................................................... University of Patras
Lacko, Andras .......................................... 321 ............................................................... University of North Texas Health Science Center at Fort Worth
Lacorazza, Daniel ....................................... 69, 82 ............................................................... Baylor College of Medicine
Lai, Stephen .............................................. 234 ............................................................... The University of Texas M.D. Anderson Cancer Center
Lai, Tsung-Po ........................................... 164 ............................................................... The University of Texas Southwestern Medical Center
Lai, Zhao ................................................... 97, 277 ............................................................... The University of Texas Health Science Center at San Antonio
Lairson, David ........................................... 226 ............................................................... The University of Texas Health Science Center at Houston
Lakshmanaswamy, Rajkumar ....................... 90 ............................................................... Texas Tech University Health Science Center at El Paso
Lamb, Candice ........................................... 324 ............................................................... The University of Texas at Austin
Lan, Zheng ............................................... 232 ............................................................... The University of Texas M.D. Anderson Cancer Center
Landi, Daniel ............................................. 263 ............................................................... Baylor College of Medicine
Lang, Frederick ......................................... 165 ............................................................... The University of Texas M.D. Anderson Cancer Center
Lantos, Cecilia ........................................... 159 ............................................................... Rice University
LaRanger, Ryan ......................................... 13, 92 ............................................................... The University of Texas Southwestern Medical Center
Larson, Jeffrey ............................................ 318 ............................................................... Salarius Pharmaceuticals LLC
Lau, Ching ............................................................... 27 ................................................. Baylor College of Medicine
Laver, Philip ......................................................... 416 ...................................................... The University of Texas Medical Branch at Galveston
Layeequr Rahman, Rakshanda .................................. 375, 419 ........................................... Texas Tech University Health Science Center at Amarillo
Le, Mimi ........................................................................ 85 ................................................. The University of Texas M.D. Anderson Cancer Center
Le, Uyen ...................................................................... 83 ................................................. The University of Texas M.D. Anderson Cancer Center
Le, Yen-Chi ................................................................... 401 ................................................. The University of Texas Health Science Center at Houston
Leal, Christina .............................................................. 358 ...................................................... The University of Texas at Austin
Leavey, Patrick ................................................................ 255 ................................................. The University of Texas Southwestern Medical Center
Lee, Brendan ................................................................. 99 ...................................................... Baylor College of Medicine
Lee, Chang-Han ............................................................ 267, 288 ........................................... The University of Texas at Austin
Lee, Ciaran .................................................................... 263 ................................................... Rice University
Lee, Dallas ...................................................................... 203 ................................................. Texas State University
Lee, Dong-Kee .................................................................. 52 ................................................. Baylor College of Medicine
Lee, Dung-Fang .............................................................. 16, 45, 65, 91 .................................. The University of Texas Health Science Center at Houston
Lee, Heng-Huan .............................................................. 298 ................................................... The University of Texas M.D. Anderson Cancer Center
Lee, J. Jack .................................................................... 23, 61 ................................................... The University of Texas M.D. Anderson Cancer Center
Lee, Jaehyuk ................................................................. 165 ...................................................... The University of Texas M.D. Anderson Cancer Center
Lee, Jason ...................................................................... 110 ................................................. The University of Texas at Austin
Lee, Jyoon ...................................................................... 232 ................................................... Rice University
Lee, Juhyeon .................................................................... 155 ................................................... The University of Texas at Austin
Lee, Ju-Seog .................................................................... 242 ................................................. The University of Texas M.D. Anderson Cancer Center
Lee, Lauren ..................................................................... 219 ................................................... Texas State University
Lee, Miles ........................................................................ 192 ................................................. Organization Not Submitted
Lee, Simon ....................................................................... 198, 214, 346, 378 ........................... The University of Texas Southwestern Medical Center
Lee, T ............................................................................. 297 ................................................... University of Houston
Lee, Tae-Kyung ............................................................... 317 ................................................... The University of Texas at Dallas
Lee, Wan-Ru ..................................................................... 317 ................................................. The University of Texas Southwestern Medical Center
Lee, Won-Chul ................................................................... 23 ................................................. The University of Texas M.D. Anderson Cancer Center
Lenkinski, Robert ............................................................. 187 ................................................. The University of Texas Southwestern Medical Center
Leonard, David ............................................................... 255 ................................................... Children’s Health, Children’s Medical Center Dallas
Lev, Dina ......................................................................... 309 ................................................... Organization Not Submitted
Levine, Herbert ................................................................ 3 ...................................................... Rice University
Levine, Robert .................................................................. 406 ................................................. Baylor College of Medicine
Lewis, Andrew .................................................................. 69, 82 ............................................ Baylor College of Medicine
Lewis, Michael ................................................................. 63, 107 ............................................ Baylor College of Medicine
Lewis-Patterson, Paula ................................................... 417 ................................................... The University of Texas M.D. Anderson Cancer Center
Li, Donghui ...................................................................... 225 ................................................. The University of Texas MD Anderson Cancer Center
Li, Feng ......................................................................... 193 ................................................... Houston Methodist
Li, Giuming ..................................................................... 230 ................................................... The University of Texas Health Science Center at San Antonio
Li, Haiyan ........................................................................ 118 ................................................... The University of Texas M.D. Anderson Cancer Center
Li, Heng ......................................................................... 173 ................................................... University of North Carolina
Li, Jian-Yuan ..................................................................... 121, 130 ...................................... Baylor College of Medicine
Li, Jun ............................................................................ 23 ...................................................... The University of Texas M.D. Anderson Cancer Center
Li, Kailong ........................................................................ 22, 88 ................................................. The University of Texas Southwestern Medical Center
Li, Liang ......................................................................... 160 ................................................... The University of Texas M.D. Anderson Cancer Center
Li, Ming .......................................................................... 342 ................................................... Texas A&M University
Li, Nan ............................................................................ 245 ................................................... The University of Texas M.D. Anderson Cancer Center
Li, Qiuli ........................................................................... 116 ................................................... The University of Texas M.D. Anderson Cancer Center
Li, Rong ............................................................................ 5, 111, 230 .................................... The University of Texas Health Science Center at San Antonio
Li, Rui ............................................................................ 317 ................................................... The University of Texas Southwestern Medical Center
Li, Tengfei ........................................................................ 173 ................................................... The University of Texas M.D. Anderson Cancer Center
Li, Wei ............................................................................ 49 ...................................................... Texas Tech University
Li, Weiwei ....................................................................... 280 ................................................... Harvard University
Li, Xiaolei ........................................................................ 253 ................................................... The University of Texas Health Science Center at San Antonio
Li, Xiao-Nan ..................................................................... 27 ...................................................... Baylor College of Medicine
Li, Yan ............................................................................... 278 ................................................. The University of Texas Health Science Center at Houston
Li, Yi ............................................................................... 52 ...................................................... Baylor College of Medicine
Li, Zheng ........................................................................... 193 ................................................... Houston Methodist
Liang, Dong ...................................................................... 156 ................................................... Texas Southern University
Liang, Yu-Chi ..................................................................... 297 ................................................... University of Houston
Liao, Hsin-Wel ................................................................... 11 ................................................. The University of Texas M.D. Anderson Cancer Center
Liao, Lan .......................................................................... 52 ...................................................... Baylor College of Medicine
Liao, Wen-Ting ................................................................. 232 ................................................... The University of Texas M.D. Anderson Cancer Center
Liao, Yiji .......................................................................... 249 ................................................... The University of Texas Health Science Center at San Antonio
Lichorad, Anna ................................................. Texas A&M University System Health Science Center
Lichtarge, Olivier ................................................. Baylor College of Medicine
Lieberman, Brandon ................................................. Organization Not Submitted
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Lin, Chun-Lin ................................................. The University of Texas Health Science Center at San Antonio
Lin, Elisa ...................................................... The University of Texas Southwestern Medical Center
Lin, John ...................................................... The University of Texas at Austin
Lin, Kevin ...................................................... The University of Texas M.D. Anderson Cancer Center
Lin, Rebecca ...................................................... John Hopkins University
Lin, Shih-Yih ...................................................... The University of Texas M.D. Anderson Cancer Center
Lin, Tsung-Chin ................................................. The University of Texas Health Science Center at Houston
Lin, Victor ........................................................ University of North Texas Health Science Center at Fort Worth
Linch, Charlie ........................................................ Texas Tech University Health Science Center
Lindsay, Holly ................................................. Baylor College of Medicine
Lines, Jefferson ...................................................... Texas Tech University Health Science Center at Amarillo
Ling, Jingjie ...................................................... The University of Texas M.D. Anderson Cancer Center
Liss, Michael ...................................................... The University of Texas Health Science Center at San Antonio
Little, Latasha ...................................................... The University of Texas M.D. Anderson Cancer Center
Litvinov, Dmitri ...................................................... University of Houston
Litvinov, Julia ...................................................... The University of Texas Medical Branch at Galveston
Litzenburger, Beate ............................................. The University of Texas M.D. Anderson Cancer Center
Liu, Arthur ...................................................... The University of Texas M.D. Anderson Cancer Center
Liu, Bin ............................................................ The University of Texas M.D. Anderson Cancer Center
Liu, Daofeng ...................................................... Baylor College of Medicine
Liu, Fuyao ...................................................... The University of Texas M.D. Anderson Cancer Center
Liu, Hsuan-Chen .................................................... Baylor College of Medicine
Liu, Jie .............................................................. Houston Methodist
Liu, Joseph ...................................................... The University of Texas Health Science Center at San Antonio
Liu, Jun ......................................................... The University of Texas Health Science Center at San Antonio
Liu, Li ............................................................. The University of Texas Southwestern Medical Center
Liu, Suyu .......................................................... The University of Texas M.D. Anderson Cancer Center
Liu, Xihui .......................................................... The University of Texas Southwestern Medical Center
Liu, Xin ............................................................. The University of Texas Southwestern Medical Center
Liu, Yangjian ...................................................... The University of Texas Southwestern Medical Center
Liu, Yen-Ting ...................................................... The University of Texas Southwestern Medical Center
Liu, Yi .............................................................. The University of Texas M.D. Anderson Cancer Center
Liu, Yuanyuan ..................................................... The University of Texas Health Science Center at Houston
Liu, Yuxuan ...................................................... The University of Texas Southwestern Medical Center
Liu, Zhongdong .................................................... Baylor College of Medicine
Liu, Zhigang ...................................................... Baylor College of Medicine
Liu, Zhijie ........................................................... The University of Texas Health Science Center at San Antonio
Livingston, Judith .................................................. The University of Texas Health Science Center at San Antonio
Lizée, Gregory ....................................................... The University of Texas M.D. Anderson Cancer Center
Lloyd, Richard ................................................. Baylor College of Medicine
Locatelli, Franco ........................................................ Organization Not Submitted
Loewen, Adam ...................................................... The University of Texas Southwestern Medical Center
Lopez, Alicia ...................................................... University of Houston
Lopez, Armando ..................................................... Lower Rio Grande Valley Area Health Education Center
Lopez, Diana ..................................................... The University of Texas Health Science Center at Houston
Lopez, Gonzalo ........................................................ Organization Not Submitted
Lopez, Melissa ..................................................... The University of Texas M.D. Anderson Cancer Center
Lopez-Berestein, Gabriel ........................................ The University of Texas M.D. Anderson Cancer Center
Lorenzi, Philip ..................................................... The University of Texas Health Science Center at Houston
Love, Latanya ..................................................... Aeglea BioTherapeutics
Lowe, David ...................................................... Val Verde Regional Medical Center
Lozano, Ceci ....................................................... Texas State University
Lozano, Ronnie .................................................... Baylor College of Medicine
Lu, Lianghao ....................................................... The University of Texas at Austin
Lu, Wei-Cheng ....................................................... Baylor College of Medicine
Lu, Xinyan ........................................................ Northwestern University Feinberg School of Medicine

159
<table>
<thead>
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<th>Name</th>
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Milbourne, Andrea ........................................... 399 ................................................. University of Texas M.D. Anderson Cancer Center
Miller, Debora ............................................. 419 .................................................... Texas Tech University Health Science Center at Amarillo
Miller, Stacie ................................................ 368, 369 ................................................. The University of Texas Southwestern Medical Center Moncrief Cancer Institute
Mills, Gordon ................................................ 7, 15, 132 ................................................. The University of Texas M.D. Anderson Cancer Center
Mills Shaw, Kenna .......................................... 132 ......................................................... The University of Texas M.D. Anderson Cancer Center
Millward, Niki ................................................ 179 ......................................................... The University of Texas M.D. Anderson Cancer Center
Milosavljevic, Aleksandar .................................. 112 ......................................................... Baylor College of Medicine
Mims, Melissa .................................................. 356 ......................................................... The University of Texas M.D. Anderson Cancer Center
Minna, John .................................................. 80, 88, 92, 104 ............................................. The University of Texas Southwestern Medical Center
Mirkovic, Dragan ............................................. 252 ......................................................... University of North Texas
Mirza Nasiri, Nooshin ....................................... 113 ......................................................... The University of Texas Health Science Center at San Antonio
Mishra, Rashika ................................................ 255 ......................................................... The University of Texas at Dallas
Misra, SM ........................................................ 357 ......................................................... Texas Children's Hospital
Mitra, Shreya ................................................... 139 ......................................................... The University of Texas M.D. Anderson Cancer Center
Mitsuya, Kohzoh ............................................... 277 ......................................................... The University of Texas Health Science Center at San Antonio
Mo, Feiyan ...................................................... 154 ......................................................... Houston Methodist
Mo, Qianxing ................................................... 25, 258 .................................................... Baylor College of Medicine
Mock, Stephen ................................................ 145 ......................................................... University of Texas at Austin
Mohamed, Ali .................................................. 319, 320 ................................................ Harvard University
Mohamedali, Khalid ......................................... 327 ......................................................... The University of Texas M.D. Anderson Cancer Center
Mohan, Radhe ................................................ 252, 269 .................................................. The University of Texas M.D. Anderson Cancer Center
Molokwu, Jennifer .......................................... 348, 349, 374 ........................................... Texas Tech University Health Science Center at El Paso
Mondal, Deboprosad ......................................... 285 ......................................................... Baylor University
Monson, Nany .................................................. 37 ......................................................... The University of Texas Southwestern Medical Center
Montalegre, Jane ............................................. 361, 383, 398 ............................................ Baylor College of Medicine
Monty, Olivier ................................................. 130 ......................................................... Baylor College of Medicine
Mooberry, Linda ............................................... 321 ......................................................... University of North Texas Health Science Center at Forth Worth
Mooney, David ................................................. 280 ......................................................... The University of Texas M.D. Anderson Cancer Center
Mooorthy, Shyam .............................................. 116 ......................................................... The University of Texas M.D. Anderson Cancer Center
Morales, Jill .................................................... 399 ......................................................... The University of Texas Health Science Center at Houston
Morales, Liza ................................................... 94 ......................................................... The University of Texas Rio Grande Valley
Morales, M. Victoria ......................................... 358 ......................................................... Nuestra Clinica Del Valle
Morales-Campos, Daisy .................................... 347, 358, 360, 362 ...................................... The University of Texas at Austin
Moralez, Patricia ............................................. 377 ......................................................... Cancer and Chronic Disease Consortium
Moran, Brett .................................................... 214 ......................................................... The University of Texas Southwestern Medical Center
Moran, Cesar .................................................. 23, 61 ......................................................... The University of Texas M.D. Anderson Cancer Center
Moran, Nancy .................................................. 217 ......................................................... Baylor College of Medicine
Moran, Thomas ............................................... 197 ......................................................... Organization Not Submitted
Moree, Shannon ............................................... 31 ......................................................... Baylor College of Medicine
Morissett, Richard ............................................. 139 ......................................................... The University of Texas at Austin
Moussalli, Micheline ........................................ 30 ......................................................... The University of Texas M.D. Anderson Cancer Center
Mu, Yunxiang .................................................. 307 ......................................................... The University of Texas M.D. Anderson Cancer Center
Mukherjee, Malini ............................................ 263 ......................................................... Baylor College of Medicine
Mukhopadhyay, Saikat ....................................... 10 ......................................................... The University of Texas Southwestern Medical Center
Muller, Florian .................................................. 232 ......................................................... The University of Texas M.D. Anderson Cancer Center
Mulu, Feven .................................................... 250 ......................................................... The University of Texas M.D. Anderson Cancer Center
Munivez, Elda ................................................... 99 ......................................................... Baylor College of Medicine
Muñoz, Edgar .................................................. 338 ......................................................... The University of Texas Health Science Center at San Antonio
Muñoz, Nina .................................................... 266 ......................................................... The University of Texas M.D. Anderson Cancer Center
Munssel, Mark ................................................ 399 ......................................................... The University of Texas M.D. Anderson Cancer Center
Murakami, Shino ............................................. 317 ......................................................... The University of Texas Southwestern Medical Center
Murphy, Caitlin ............................................... 408 ......................................................... The University of Texas Southwestern Medical Center
Murphy, Hope .................................................. 93 ......................................................... Texas Christian University
Murray, Jeffrey ................................................ 27, 143 .................................................... Cook Children's Medical Center
Musher, Benjamin ........................................... 398 ......................................................... Baylor College of Medicine
Muthuswamy, Senthil ....................................... 250 ......................................................... Organization Not Submitted
Muzny, Donna .................................................. 40 ......................................................... Baylor College of Medicine
Myers, Jeffrey ................................................ 64, 116 .................................................... The University of Texas M.D. Anderson Cancer Center
Nagi, Chandandeep ........................................... 63 ......................................................... Baylor College of Medicine
Nagrath, Deepak ............................................. 232 ......................................................... The University of Texas M.D. Anderson Cancer Center
Naing, Aung ................................................... 421 ......................................................... The University of Texas M.D. Anderson Cancer Center
Nair, Amritha .................................................... 63 ......................................................... Baylor College of Medicine
Nakada, Daisuke .............................................. 19 ......................................................... Baylor College of Medicine
Narayan, Aditi .................................................. 418 ......................................................... LIVESTRONG
<table>
<thead>
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163
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<td>Pontremoli, Mila</td>
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<td>Powell, Reid</td>
<td>Texas A&amp;M University Health Science Center Institute of Biosciences and Technology</td>
</tr>
<tr>
<td>Pownall, Henry</td>
<td>Houston Methodist</td>
</tr>
</tbody>
</table>
Pozo, Karine .................................................. 80 The University of Texas Southwestern Medical Center
Pozos, Helen ............................................. 368, 369 The University of Texas Southwestern Medical Center Moncrief Cancer Institute
Prakash, Priyanka ........................................ 239 The University of Texas Health Science Center at Houston
Prasad, Saurabh ........................................... 182 University of Houston
Pratt, Kathy ..................................................... 389 The University of Texas Southwestern Medical Center
Prebisch, Ana .............................................. 171 The University of Texas Health Science Center at Houston
Price, Andrea ................................................ 350 Organization Not Submitted
Priebe, Waldemar ......................................... 273 The University of Texas M.D. Anderson Cancer Center
Prisacariu, Adrian .......................................... 302, 303 VisionSR, Inc.
Prohaska, David ........................................... 311 Instituto de Biología y Medicina Experimental
Proietti, Cecilia J. ........................................... 249 The University of Texas Southwestern Medical Center
Pruitt, Sondi .................................................... 210, 228 The University of Texas Health Science Center at Houston
Pruthi, Deepak ............................................. 241 The University of Texas Health Science Center at Houston
Prykhodko, Amberly ...................................... 390 The University of Texas Southwestern Medical Center
Pudakalakatti, Shivanand ................................ 179, 199, 276 The University of Texas M.D. Anderson Cancer Center
Pungaruru, Sureshwar .................................... 235, 237 Texas Tech University Health Science Center at Amarillo
Puppi, Monica .................................................. 69 Baylor College of Medicine
Putkey, John ................................................... 239 The University of Texas Health Science Center at Houston
Putluri, Nagireddy ........................................... 152, 234 Baylor College of Medicine
Putluri, Vasanta ............................................. 234 Baylor College of Medicine
Putnam, Trey .................................................. 131 Texas Tech University Health Science Center at Dallas
Qi, Le ................................................................. 22 The University of Texas Southwestern Medical Center
Qi, Lin .............................................................. 27 Baylor Research Institute
Qi, Yutao .......................................................... 257 University of Houston
Qin, Li ............................................................... 53 Baylor College of Medicine
Qin, Qin .............................................................. 208 Xiang-Ya Hospital of Central South University
Qiu, Wenlan ..................................................... 297 University of Houston
Quang, Timothy ................................................ 170 Rice University
Quek, Kelly ..................................................... 23 The University of Texas M.D. Anderson Cancer Center
Quintana, Jeremy ............................................ 291 Baylor University
Quirk, Lisa ...................................................... 198, 346, 352, 353, 355, 393, 395 The University of Texas Southwestern Medical Center
Qureshi, Adnan .............................................. 246 The University of Texas at Arlington
Qutub, Amina .................................................. 159 Rice University
Rabin, Karen ................................................... 238 Baylor College of Medicine
Radwan, Mohamed ......................................... 139 Organization Not Submitted
Raines Milenkov, Amy .................................... 387 University of North Texas Health Science Center at Fort Worth
Rainusso, Nino ............................................... 114, 326 Baylor College of Medicine
Raj, Ganesh ..................................................... 317 The University of Texas Southwestern Medical Center
Raja, Balakrishnan ......................................... 192 University of Houston
Rajapakse, Kimal ........................................... 147, 152 Baylor College of Medicine
Raji, Idris .......................................................... 135, 136, 137 Baylor College of Medicine
Rakheja, Dinesh ............................................. 255 The University of Texas Southwestern Medical Center
Ramalingam, Harini ....................................... 58 The University of Texas Southwestern Medical Center
Ramamurthy, Uma ......................................... 143 Baylor College of Medicine
Ramdan, Raghad ............................................ 296 Organization Not Submitted
Ramirez, Amelie ............................................ 338 The University of Texas Southwestern Medical Center
Ramirez, Michael ............................................ 92 The University of Texas Health Science Center at San Antonio
Ramondetta, Lois ........................................... 356 The University of Texas Southwestern Medical Center
Ranganna, Kasturi .......................................... 293 Texas Southern University
Rangel, Lizette ............................................... 412 The University of Texas M.D. Anderson Cancer Center
Ranjan, Amalendu ........................................... 248 University of North Texas Health Science Center at Fort Worth
Rao, Arvind ...................................................... 148, 153 The University of Texas M.D. Anderson Cancer Center
Rao, Wei .......................................................... 206, 207, 256, 257 The University of Texas Health Science Center at Houston
Rao, Xiayu ....................................................... 116 The University of Texas M.D. Anderson Cancer Center
Raut, Sangram ............................................... 321 University of North Texas Health Science Center at Fort Worth
Raza, Syed-Ahsan ........................................... 222 Baylor College of Medicine
Rechis, Ruth .................................................... 363 The University of Texas M.D. Anderson Cancer Center
Reddick, Robert ............................................. 97 The University of Texas Health Science Center at San Antonio
Redell, Michele ............................................... 258 Baylor College of Medicine
Reed, Damon ................................................... 323 H. Lee Moffitt Cancer Center and Research Institute
Rees, Terry ....................................................... 169 Texas A&M University System Health Science Center
Reineke, Lucas .................................................. 25 Baylor College of Medicine
Reinhardt, Carsten ......................................... 319, 320 Immatics Biotechnologies
Reininger, Belinda .......................................... 399 The University of Texas Health Science Center at Houston
<table>
<thead>
<tr>
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<td>Baylor College of Medicine</td>
</tr>
</tbody>
</table>
Salinas, Jennifer ........................................ 376 ........................................ The University of Texas Health Science Center at El Paso
Salmi, Mari ........................................ 306 ........................................ Paratus Diagnostics
Salzillo, Travis ........................................ 165 ........................................ The University of Texas M.D. Anderson Cancer Center
Sammons, Rachel ....................................... 142 ........................................ The University of Texas at Austin
Samoylova, Olga ......................................... 14 ........................................ The University of Texas Medical Branch at Galveston
Samuel, Errol ........................................ 137 ........................................ Baylor College of Medicine
San Lucas, F. Anthony ................................. 167, 181, 183 ........................................ The University of Texas M.D. Anderson Cancer Center
San Martin, Rebecca .................................... 107 ........................................ Baylor College of Medicine
San Miguel, Yazmin ..................................... 229 ........................................ The University of Texas M.D. Anderson Cancer Center
Sanber, Khaled ......................................... 263 ........................................ Baylor College of Medicine
Sanchez, Marivel ....................................... 382 ........................................ Texas A&M University System Health Science Center
Sanchez, Nora .......................................... 132 ........................................ The University of Texas M.D. Anderson Cancer Center
Sanders, Joanne ....................................... 395 ........................................ The University of Texas Southwestern Medical Center
Sanders, Mark ......................................... 213 ........................................ The University of Texas Health Science Center at Houston
Sandulache, Vlad .................................... 234 ........................................ Baylor College of Medicine
Sangi, Haleh ........................................... 361 ........................................ Texas Childrens Hospital
Santa Maria, Diane ..................................... 357 ........................................ The University of Texas Health Science Center at Houston
Santini, Conrad ......................................... 130, 135, 136, 137 ........................................ Parkland Health and Hospital System
Santini, Noel ........................................... 198, 214, 408 ........................................ Baylor College of Medicine
Santos, Luz ........................................... 375 ........................................ Texas Tech University Health Science Center at Amarillo
Sareddy, Gangadhar Reddy ......................... 317 ........................................ The University of Texas Health Science Center at San Antonio
Sarkar, Asis ........................................... 310 ........................................ Baylor College of Medicine
Sarkar-Banerjee, Suparna ............................ 239 ........................................ The University of Texas Health Science Center at San Antonio
Sarker, Marjana ........................................ 248 ........................................ University of North Texas Health Science Center at Fort Worth
Sarpong, Kwabena ..................................... 336 ........................................ The University of Texas Medical Branch at Galveston
Satani, Nikunj .......................................... 232 ........................................ The University of Texas M.D. Anderson Cancer Center
Satelli, Arun ........................................... 319, 320 ........................................ Immatics Biotechnologies
Satsangi, Arpan ........................................ 241 ........................................ The University of Texas Health Science Center at San Antonio
Savas, Lara ........................................... 200, 204, 209, 211, 226, 356, 377, 402 ........................................ The University of Texas Health Science Center at Houston
Sawakuchi, Gabriel ................................ 243 ........................................ The University of Texas M.D. Anderson Cancer Center
Sayre, James .......................................... 262 ........................................ Organization Not Submitted
Scaglioni, Pier P ....................................... 104 ........................................ The University of Texas Southwestern Medical Center
Schaeftzle, Sebastian ................................ 288 ........................................ The University of Texas at Austin
Schect, Paul ........................................... 181, 183 ........................................ The University of Texas M.D. Anderson Cancer Center
Scheurer, Michael ..................................... 143, 238, 361, 413 ........................................ Baylor College of Medicine
Schick, Vanessa ....................................... 401 ........................................ The University of Texas Health Science Center at Houston
Schiff, Rachel .......................................... 63 ........................................ Baylor College of Medicine
Schmeler, Kathleen ................................... 351, 399 ........................................ The University of Texas M.D. Anderson Cancer Center
Schmid, Vanessa ..................................... 58 ........................................ The University of Texas Southwestern Medical Center
Schneider, John ....................................... 218 ........................................ University of Chicago Medicine
Schoor, Oliver ......................................... 319, 320 ........................................ Immatics Biotechnologies
Schraw, Jeremy ....................................... 238 ........................................ Baylor College of Medicine
Schultz, Robbie ....................................... 138 ........................................ The University of Texas Health Science Center at Houston
Schwarz, Richard ..................................... 170 ........................................ Rice University
Scott, Kenneth ......................................... 7 ........................................ Baylor College of Medicine
Scott, Larry ........................................... 398 ........................................ The University of Texas Health Science Center at Houston
Scott, Robert .......................................... 278 ........................................ Texas State University
Seiler, Stephen ....................................... 187 ........................................ The University of Texas Southwestern Medical Center
Selvar, Chelliah ....................................... 293 ........................................ Texas Southern University
Sen, Arun ............................................ 221 ........................................ Texas A&M University
Sengupta, Anita ....................................... 255 ........................................ The University of Texas Southwestern Medical Center
Sepesi, Boris ........................................... 61 ........................................ The University of Texas M.D. Anderson Cancer Center
Sephan, Clifford ..................................... 27 ........................................ Texas A&M University Health Science Center Institute of Biosciences and Technology
Sessler, Jonathan ..................................... 316 ........................................ The University of Texas at Austin
Shah, Krishna ......................................... 245 ........................................ The University of Texas M.D. Anderson Cancer Center
Shaiken, Tatyf ......................................... 86 ........................................ Peri-Nuc Labs LLC
Sharkey, Francis ...................................... 18 ........................................ The University of Texas Health Science Center at San Antonio
Shaw, Chad ........................................... 63 ........................................ Baylor College of Medicine
Shay, Jerry ............................................ 13, 92, 164 ........................................ The University of Texas Southwestern Medical Center
Shay, Laura ............................................ 414, 417 ........................................ The University of Texas Health Science Center at Houston
Shegog, Ross .......................................... 209, 211, 226 ........................................ The University of Texas Health Science Center at Houston
Shem, Eun Yong ....................................... 420 ........................................ The University of Texas Health Science Center at San Antonio
Shen, Jianjun .......................................... 149, 150 ........................................ The University of Texas M.D. Anderson Cancer Center
Shen, Ye .............................................. 69 ........................................ Baylor College of Medicine

167
Sheng, Jie ......................................................... 245 ................................. The University of Texas M.D. Anderson Cancer Center
Sheng, Kuanwei .................................................. 63 ................................. Baylor College of Medicine
Sheppard, Hadley .................................................. 74 ................................. Baylor College of Medicine
Sheridan, Richard .................................................. 311 ................................. Aravive Biologics
Sherry, Dean ......................................................... 227 ................................. The University of Texas Southwestern Medical Center
Shi, Colin ............................................................. 298 ................................. The University of Texas M.D. Anderson Cancer Center
Shi, Xiaobing ......................................................... 12 ................................. The University of Texas M.D. Anderson Cancer Center
Shi, Zhe ............................................................. 285 ................................. Baylor University
Shih, Wei-Chuan ..................................................... 84 ................................. University of Houston
Shim, Eun Yong ....................................................... 253 ................................. The University of Texas Health Science Center at San Antonio
Shimada, Issei ......................................................... 10 ................................. The University of Texas Southwestern Medical Center
Shin, Ji-Hyun .......................................................... 242 ................................. The University of Texas M.D. Anderson Cancer Center
Shin, Seung Jun ....................................................... 50 ................................. The University of Texas M.D. Anderson Cancer Center
Shinbrot, Eve ......................................................... 116 ................................. The University of Texas M.D. Anderson Cancer Center
Shinn, Eileen .......................................................... 412, 415 ................................. The University of Texas M.D. Anderson Cancer Center
Shivachar, Amruthesh ............................................... 293 ................................. Texas Southern University
Shohet, Elliot .......................................................... 413 ................................. Texas Childrens Hospital
Shohet, Jason .......................................................... 47 ................................. Baylor College of Medicine
Shokar, Navkiran ...................................................... 348, 349, 371, 373, 374, 376 ................................. Texas Tech University Health Science Center at El Paso
Sholl, Andrew ........................................................ 117 ................................. Organization Not Submitted
Shouman, Samia ...................................................... 296 ................................. Organization Not Submitted
Shree, Sonakshree .................................................... 344 ................................. University of Houston
Shrestha, Ramesh ..................................................... 194 ................................. University of North Texas
Shu, Hai ............................................................... 46 ................................. The University of Texas M.D. Anderson Cancer Center
Shuck, Ryan .......................................................... 326 ................................. Baylor College of Medicine
Shufeian, Md Abu .................................................... 132 ................................. The University of Texas M.D. Anderson Cancer Center
Shukla, Girja ........................................................... 288 ................................. University of Vermont
Shureiqi, Imad ........................................................ 30 ................................. The University of Texas M.D. Anderson Cancer Center
Siceluff, Andrea ..................................................... 402 ................................. The University of Texas Health Science Center at Houston
Siddik, Zahid .......................................................... 316 ................................. The University of Texas M.D. Anderson Cancer Center
Sidhu, Stan ............................................................. 178 ................................. University of Sydney
Sidiropoulos, Nikoletta ............................................ 288 ................................. University of Vermont
Sieger, Kerry .......................................................... 319, 320 ................................. Immatics Biotechnologies
Sieglafl, Douglas ...................................................... 32 ................................. Houston Methodist
Sikora, Andrew ....................................................... 107, 197, 280, 290, 291, 292, 294 ................................. Baylor College of Medicine
Silva, Noe ............................................................. 358 ................................. Nuestra Clinica Del Valle
Silvestrov, Pavel ...................................................... 188 ................................. University of North Texas
Simmons, Denise Perry ............................................ 194, 270 ................................. University of North Texas
Simmons, Nicholas .................................................. 130 ................................. Baylor College of Medicine
Simon, Callie ......................................................... 216 ................................. The University of Texas M.D. Anderson Cancer Center
Simper, Melissa ...................................................... 150 ................................. The University of Texas M.D. Anderson Cancer Center
Simpson, Amy ......................................................... 132 ................................. The University of Texas M.D. Anderson Cancer Center
Singal, Amit .......................................................... 191, 346, 352, 353, 355, 393, 395, 397, 408 ................................. The University of Texas Southwestern Medical Center
Singh, Harpreet ......................................................... 319, 320 ................................. Immatics Biotechnologies
Sintes-Yallen, Amanda ............................................... 391 ................................. The University of Texas Health Science Center at Houston
Sivakumar, Smruthy .................................................. 181, 183 ................................. The University of Texas M.D. Anderson Cancer Center
Szemere, Elizabeth ............................................... 93, 286 ................................. Texas Christian University
Skapek, Stephen ....................................................... 35, 95, 172 ................................. The University of Texas Southwestern Medical Center
Skeparnias, Ilias ....................................................... 325 ................................. University of Patras
Skillern, Wesley ....................................................... 208 ................................. Boston Children’s Hospital
Skinner, Celette ....................................................... 408, 411 ................................. The University of Texas Southwestern Medical Center
Skordilas, Andreas .................................................... 325 ................................. University of Athens
Sladek, Frances ....................................................... 106 ................................. University of California Riverside
Slater, John ........................................................... 265 ................................. Organization Not Submitted
Slavine, Nikolai ....................................................... 187 ................................. The University of Texas Southwestern Medical Center
Slebos, Robbert ....................................................... 112 ................................. Vanderbilt University
Smith, Holly ......................................................... 213 ................................. The University of Texas Health Science Center at Houston
Smith, Sabrina ....................................................... 230 ................................. The University of Texas Health Science Center at San Antonio
Smits, Jasper ......................................................... 223 ................................. The University of Texas at Austin
Sobieski, Mary ....................................................... 27 ................................. Texas A&M University Health Science Center Institute of Biosciences and Technology
Sohn, Bohwa ......................................................... 242 ................................. The University of Texas M.D. Anderson Cancer Center
Sokolov, Konstantin .................................................. 304, 331 ................................. The University of Texas M.D. Anderson Cancer Center
Soldi, Raffaella ......................................................... 309, 318 ................................. Beta Cat Pharmaceuticals, LLC
Sloe, Cindy ............................................................ 418 ................................. Organization Not Submitted
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<td>Texas Tech University Health Sciences Center</td>
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<td>Wang, Dong</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
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<td>Baylor College of Medicine</td>
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<td>Baylor College of Medicine</td>
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<td>Baylor College of Medicine</td>
</tr>
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<td>Baylor College of Medicine</td>
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<td>The University of Texas at Austin</td>
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<td>Baylor Research Institute</td>
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<td>Wang, Lisa</td>
<td>Baylor College of Medicine</td>
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<td>Baylor College of Medicine</td>
</tr>
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<td>Wang, Shan</td>
<td>University of Houston</td>
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<td>Baylor College of Medicine</td>
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<td>Wang, Wenyi</td>
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<td>Purdue University</td>
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<td>Wang, Xiaojing</td>
<td>Baylor College of Medicine</td>
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<td>Baylor University</td>
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<td>University of North Carolina</td>
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<td>Rice University</td>
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Yang, Liuqing .................................. 105 .................................................. The University of Texas M.D. Anderson Cancer Center
Yang, Mei .................................. 249 .................................................. The University of Texas Health Science Center at San Antonio
Yang, Zhen .................................. 193 .................................................. Houston Methodist
Yao, Tingfeng .................................. 163 .................................................. The University of Texas at Arlington
Yao, Yuan .................................. 258 .................................................. Baylor College of Medicine
Yap, Timothy .................................. 132 .................................................. The University of Texas M.D. Anderson Cancer Center
Yee, Cassian .................................. 320 .................................................. The University of Texas M.D. Anderson Cancer Center
Yeh, Yulu .................................. 341, 342 .................................................. Texas A&M University
Yek, Christina .................................. 352 .................................................. The University of Texas Southwestern Medical Center
Yellapragada, Sarvari .................................. 31 .................................................. Baylor College of Medicine
Yen, Laising .................................. 4 .................................................. Rice University
Yepes, Pablo .................................. 252 .................................................. The University of Texas Health Science Center at San Antonio
Yi, Song .................................. 51 .................................................. The University of Texas M.D. Anderson Cancer Center
Yin, Jun .................................. 15 .................................................. The University of Texas M.D. Anderson Cancer Center
Yin, Xue .................................. 1 .................................................. The University of Texas Health Science Center at San Antonio
Yin, Yizhi .................................. 57 .................................................. The University of Texas at Austin
Yin, Zenong .................................. 350 .................................................. The University of Texas Health Science Center at San Antonio
Ying, Haoqiang .................................. 232 .................................................. The University of Texas M.D. Anderson Cancer Center
Yi-Shing, Lisa .................................. 175 .................................................. Texas A&M University System Health Science Center
Yong, QianChen .................................. 291 .................................................. Organization Not Submitted
Yong-Fang, Kuo .................................. 351 .................................................. The University of Texas Medical Branch at Galveston
Yoo, Seung-Hee .................................. 106 .................................................. The University of Texas Health Science Center at Houston
Yoon, David .................................. 243 .................................................. The University of Texas M.D. Anderson Cancer Center
York, Brian .................................. 66 .................................................. Baylor College of Medicine
You, Yanan .................................. 102 .................................................. The University of Texas Health Science Center at Houston
Young, Damian .................................. 130, 135, 136, 137 .................................................. Baylor College of Medicine
Young, Simon .................................. 280 .................................................. The University of Texas Health Science Center at Houston
Yu, Kaixian .................................. 50, 173 .................................................. The University of Texas M.D. Anderson Cancer Center
Yu, Shuai .................................. 163 .................................................. The University of Texas at Arlington
Yu, Wangjie .................................. 234 .................................................. Baylor College of Medicine
Yu, Wendong .................................. 178 .................................................. Baylor College of Medicine
Yu, Xiaobin .................................. 53 .................................................. Baylor College of Medicine
Yu, Xiaojie .................................. 48, 100 .................................................. The University of Texas Health Science Center at San Antonio
Yu, Zifeng .................................. 130 .................................................. Baylor College of Medicine
Yuan, Baohong .................................. 163 .................................................. The University of Texas at Arlington
Yuan, Bin .................................. 5, 111, 230 .................................................. The University of Texas Health Science Center at San Antonio
Yuan, Xiao-Jun .................................. 27 .................................................. Xinhua Children’s Hospital
Yum, Jeong Eun .................................. 139 .................................................. The University of Texas at Austin
Yustein, Jason .................................. 99, 114, 326 .................................................. Baylor College of Medicine
Zacharias, Niki .................................. 165 .................................................. The University of Texas M.D. Anderson Cancer Center
Zaidi, Tanweer .................................. 177 .................................................. The University of Texas M.D. Anderson Cancer Center
Zaki, Hasan .................................. 20 .................................................. The University of Texas Southwestern Medical Center
Zal, Anna .................................. 245 .................................................. The University of Texas M.D. Anderson Cancer Center
Zal, Tomasz .................................. 245 .................................................. The University of Texas M.D. Anderson Cancer Center
Zang, Tianwu .................................. 123 .................................................. Baylor College of Medicine
Zelazowska, Monika .................................. 307 .................................................. The University of Texas M.D. Anderson Cancer Center
Zeng, Huan-Chang .................................. 99 .................................................. Baylor College of Medicine
Zeng, Jia .................................. 132 .................................................. The University of Texas M.D. Anderson Cancer Center
Zeng, Zhiquan .................................. 96 .................................................. The University of Texas Southwestern Medical Center
Zeng, Zihua .................................. 171 .................................................. Houston Methodist
Zermeno Nava, Jose de Jesus .................................. 190 .................................................. Hospital Central Dr. Ignacio Morones Prieto
Zewdu, Abeba .................................. 309 .................................................. Organization Not Submitted
Zhang, Alee .................................. 315 .................................................. The University of Texas Southwestern Medical Center
Zhang, Bing .................................. 63, 70, 109, 112 .................................................. Baylor College of Medicine
Zhang, Changsheng .................................. 155 .................................................. The University of Texas at Austin
Zhang, Chi .................................. 111 .................................................. The University of Texas Health Science Center at San Antonio
Zhang, Huaiyuan .................................. 27 .................................................. Baylor College of Medicine
Zhang, Jialing .................................. 178 .................................................. The University of Texas at Austin
Zhang, Jianhua .................................. 23 .................................................. The University of Texas M.D. Anderson Cancer Center
Zhang, Jianjun .................................. 23, 61 .................................................. The University of Texas M.D. Anderson Cancer Center
Zhang, Jiejin .................................. 23, 116 .................................................. The University of Texas M.D. Anderson Cancer Center
Zhang, Li .................................. 21 .................................................. The University of Texas at Dallas
Zhang, Michelle .................................. 324 .................................................. Organization Not Submitted
Zhang, Nenggang .................................. 310 .................................................. Baylor College of Medicine
Zhang, Ning ................................................................. The University of Texas Southwestern Medical Center
Zhang, Ningyan ......................................................... The University of Texas Health Science Center at Houston
Zhang, Peng .............................................................. The University of Texas M.D. Anderson Cancer Center
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Zhang, Xinyi ............................................................... The University of Texas Southwestern Medical Center
Zhang, Yanting ............................................................. University of Houston
Zhang, Yiqiang ............................................................ The University of Texas Health Science Center at Houston
Zhang, Yonghong ........................................................... The University of Texas Rio Grande Valley
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Zhu, Ning ................................................................. Baylor University
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Zolekar, Ashwini ......................................................... University of North Texas Health Science Center at Fort Worth
Zong, Chenghang ........................................................ Baylor College of Medicine
Zoorob, Roger ............................................................ Baylor College of Medicine
Zu, Youli ................................................................. Houston Methodist
Zuniga, Krystle ............................................................ Texas State University
Zuo, Xiangsheng .......................................................... The University of Texas M.D. Anderson Cancer Center
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