17th Annual
Zubrod Memorial Lecture
& Sylvester Cancer Research Poster Session
Tuesday, May 10, 2016
Lois Pope LIFE Center Auditorium
Schoninger Research Quadrangle
Charles Gordon Zubrod, M.D., received his Bachelor of Arts degree from Holy Cross College in Boston in 1936, and his medical degree from the College of Physicians and Surgeons of Columbia University in New York in 1940. During World War II, he joined the U.S. Army and was assigned to Dr. James A. Shannon’s staff in the Malaria Project at the Goldwater Memorial Hospital in New York. While there, he was introduced to clinical research in infectious diseases and pharmacology. Dr. Zubrod later joined the National Institutes of Health as Chief of the General Medicine Branch of the National Cancer Institute (NCI) where he spent 14 years as its Clinical and Scientific Director. He completed his service as the Division of Cancer Treatment Director.

At the NCI, Dr. Zubrod’s training in pharmacology and experience as a clinical investigator gave him the background to develop the institute’s chemotherapy research program. It was under his direction that the successful treatment of acute leukemia in childhood was developed, as was the treatment of Hodgkin lymphoma. Dr. Zubrod introduced the randomized control trial into the evaluation of new treatment regimens and created the first of the national cooperative clinical trials groups. Due to his prodigious efforts, he has been called the “father of cancer chemotherapy.”

In 1974, Dr. Zubrod joined the University of Miami as the Director of its fledgling cancer center and the Chairman of the Department of Oncology. He developed a strong research program with basic and clinical components and programs in outreach and early detection. Dr. Zubrod was instrumental in the acquisition of the generous Sylvester gift, which led to the naming of Sylvester Comprehensive Cancer Center.

The Annual Zubrod Memorial Lecture, part of the Distinguished Lecture Series, is held to honor Charles Gordon Zubrod, M.D., a devoted physician-scientist, extraordinary leader, and a valued colleague who set high standards in order to create a center of excellence at Sylvester Comprehensive Cancer Center.
An internationally recognized authority on the genetic basis of human cancer, Robert A. Weinberg, Ph.D., is a founding member of the Whitehead Institute for Biomedical Research and the Daniel K. Ludwig Professor for Cancer Research at the Massachusetts Institute of Technology (MIT). He is also the first Director of the Ludwig Center for Molecular Oncology at MIT.

During the past three decades, Dr. Weinberg has made breakthrough discoveries in the molecular and genetic roots of cancers. His lab discovered the first oncogene in 1982 and the first tumor suppressor gene in 1986. Most recently, Dr. Weinberg and his colleagues were the first to define the genetic rules that must be followed in order for a normal human cell to be transformed into a human cancer cell.

Dr. Weinberg’s lab is primarily concerned with how oncogenes, their normal counterparts (proto-oncogenes) and tumor suppressor genes fit together in the complex circuitry that controls cell growth. His lab recently succeeded in creating the first genetically defined human cancer cells. Dr. Weinberg is particularly interested in applying this knowledge to improve the diagnosis and treatment of breast cancer. Currently, his lab seeks to understand how a malicious population of tumor cells, called cancer stem cells, develop their metastatic powers and what biological conditions are required to eliminate them.

Author or editor of six books and more than 420 articles, Dr. Weinberg is best known for his comprehensive cancer textbook “The Biology of Cancer.” His other books, intended for a lay audience, are “One Renegade Cell,” “Racing to the Beginning of the Road: The Search for the Origin of Cancer” and “Genes and the Biology of Cancer,” co-authored with Dr. Harold E. Varmus, former Director of the National Institutes of Health.

Dr. Weinberg is an elected Member of the U.S. National Academy of Sciences and a Fellow of the American Academy of Arts and Sciences. He is also a Member of the American Philosophical Society and the Institute of Medicine. He has received the National Medal of Science (1997), the Wolf Prize in Medicine (2007), the Otto Warburg Medal (2007) and the Breakthrough Prize in Life Sciences (2013).
2015
Arul M. Chinnaiyan, M.D., Ph.D.
The Application of Integrative Sequencing for Precision Oncology

2014
Kenneth C. Anderson, M.D.
New Insights into Therapeutic Targets in Multiple Myeloma

2013
James R. Downing, M.D.
The Pediatric Cancer Genome Project – Implications of Clinical Medicine

2012
Ronald Levy, M.D.
Immunotherapy of Lymphoma

2011
Vishva Dixit, M.D.
Lessons from Death Signaling

2010
Mario R. Capecchi, Ph.D.
Modeling Human Cancer in the Mouse

2009
Bert W. O’Malley, M.D.
Nuclear Receptor Coactivators: “Master Genes” and Targets of Disease

2008
Tyler Jacks, Ph.D.
Modeling Cancer in the Mouse

2007
Susan Band Horwitz, Ph.D.
Taxol, Tubulin and Tumors: Challenges in the New Era of Chemotherapy

2006
Judah Folkman, M.D.
Lessons from Antiangiogenic Therapy and Other Diseases

2005
Rainer F. Storb, M.D.

2004
Carlos L. Arteaga, M.D.
From Sarcoma Growth Factor to TGF-beta Targeted Therapeutics in Human Neoplasia

2003
Ralph M. Steinman, M.D.
The Control of Immunity and Tolerance by Dendritic Cells

2002
Stanley Korsmeyer, M.D.
Mitochondrial Gateway to Apoptosis
2016 Outstanding Faculty Awards

Basic Scientist of the Year

**Stephen Lee, Ph.D.**
Leader, Tumor Biology Research Program, Sylvester Comprehensive Cancer Center | Professor, Department of Biochemistry and Molecular Biology, Miller School of Medicine

Dr. Stephen Lee earned his doctoral degree in experimental medicine from McGill University and trained as a postdoctoral fellow in the laboratory of Dr. Richard Klaunser at the National Cancer Institute. He was a Professor of Cellular and Molecular Medicine at the University of Ottawa for 15 years prior to joining Sylvester. He discovered a class of long noncoding RNA that regulates the cellular mobility of molecules and an alternative translation machinery that synthesizes proteins in the absence of oxygen. His NCI-funded research program focuses on understanding the mechanisms of tumor cell dormancy. He currently serves as the Leader of the Tumor Biology Research Program and as Chair of the Scientific Advisory Board at Sylvester.

Clinical Researcher of the Year

**Ronan Swords, M.D., Ph.D., FRCPI, FRCPath**
Clinical Program Leader, Cancer Epigenetics Programs, Sylvester Comprehensive Cancer Center | Co-leader, Phase I Program | Pap Corps Endowed Professor in Leukemia | Assistant Professor, Division of Hematology/Oncology, Miller School of Medicine

Dr. Ronan Swords completed his residency and fellowship training in hematology/oncology in Ireland and the UK (Royal College of Physicians of Ireland, Royal College of Pathologists, London). He received additional fellowship training in new drug development at the University of Texas Health Science Center in San Antonio, where he also completed his doctoral thesis in pharmacology and acute leukemia. In 2012, he joined Sylvester, where he has helped to build and develop the adult leukemia service. His NCI-funded research is focused on developing new approaches for acute myeloid leukemia (AML) and related diseases. He has a particular interest in studying protein neddylation pathways and epigenetic modulation in AML.

Community-Based Researcher of the Year

**Judith Hurley, M.D.**
Member, Sylvester Comprehensive Cancer Center | Professor, Division of Hematology/Oncology, Miller School of Medicine | Medical Director of the Hematology/Oncology Clinics at Jackson Memorial Hospital | Consultant Medical Oncologist, Taylor Breast Health Center at Jackson Memorial Hospital

Dr. Judith Hurley is a board-certified oncologist who specializes in breast cancer. She obtained her undergraduate degree at Yale University, her medical degree and residency at SUNY-Upstate and fellowship training at New York University. Her research interest focuses on the problems faced by underserved women with breast cancer including understanding the disparities faced by this group, looking for predictive factors in triple-negative breast cancer, evaluating genetic risk in Caribbean women with breast cancer, pain management in minority populations, the effect of diet and obesity on the relapse of triple-negative breast cancer, the treatment of locally advanced breast cancer and women with breast cancer and HIV.
Dipen J. Parekh, M.D.
Member, Sylvester Comprehensive Cancer Center | Professor and Chairman, Department of Urology, Miller School of Medicine | Director of Robotic Surgery

Dr. Dipen J. Parekh is a board-certified, fellowship-trained urologist specializing in urologic oncology using minimally invasive laparoscopic, robotic and traditional open approaches to treating prostate, bladder and kidney cancer. He is recognized nationally and internationally for his surgical and research accomplishments, having performed more than 4,000 robotic urologic procedures and serving as Principal Investigator on numerous clinical trials. Having benefited from outstanding mentors early in his career, since arriving at Sylvester, Dr. Parekh has focused on recruiting and mentoring junior faculty members during the most critical periods in their professional development.

James E. Hoffman, M.D.
Director, Outpatient Clinics, Sylvester Comprehensive Cancer Center | Assistant Professor, Division of Hematology/Oncology, Miller School of Medicine | Associate Director, Hematology/Oncology Fellowship Program | Director, Myeloma and Amyloidosis Program

Dr. James Hoffman earned his bachelor’s degree from Columbia University and his medical degree from Albert Einstein College of Medicine. He completed his internship, residency and chief residency at New York University and fellowship in hematology/oncology at Memorial Sloan-Kettering Cancer Center. His research interests focus on clinical trials for multiple myeloma and amyloidosis. He gives regular lectures on campus to medical students, residents and fellows.

Kerry L. Burnstein, Ph.D.
Associate Director, Education and Training, Sylvester Comprehensive Cancer Center | Professor, Department of Molecular & Cellular Pharmacology, Miller School of Medicine

Dr. Kerry Burnstein is deeply committed to the education and training of the next generation of cancer researchers and physicians. She develops curricula and participates in a variety of pedagogical approaches for graduate and medical students. Dr. Burnstein has mentored 14 graduate students, most of whom are pursuing careers in oncology research and education. She maintains an active research program focusing on androgen receptor signaling and novel experimental therapeutics for metastatic prostate cancer.
### Past Outstanding Faculty Awards

#### 2015 Basic Scientist of the Year
- **Ronald C. Desrosiers, Ph.D.**
  - Member, Sylvester Comprehensive Cancer Center | Professor, Department of Pathology, Miller School of Medicine | Director, Research Faculty Development

#### 2015 Mentor of the Year – Junior Faculty
- **Jonathan C. Trent, M.D., Ph.D.**
  - Co-director, Musculoskeletal Center, Sarcoma Medical Research Program, Sylvester Comprehensive Cancer Center | Professor, Division of Hematology/Oncology, Miller School of Medicine

#### 2015 Clinical Researcher of the Year
- **Alan Pollack, M.D., Ph.D.**
  - Co-leader, NRG GU Translational Research Program, Sylvester Comprehensive Cancer Center | Professor and Chairman, Department of Radiation Oncology, Miller School of Medicine | Service Chief, Radiation Oncology, Jackson Memorial Hospital

#### 2015 Mentor of the Year – Trainees
- **Vinata B. Lokeshwar, Ph.D.**
  - Member, Sylvester Comprehensive Cancer Center | Professor, Department of Urology, Miller School of Medicine

#### 2015 Community-Based Researcher of the Year
- **Erin Kobetz, Ph.D., M.P.H.**
  - Associate Director, Disparities and Community Outreach, Sylvester Comprehensive Cancer Center | Program Leader, Cancer Prevention Control and Survivorship | Director, Jay Weiss Institute for Health Equity | Associate Professor, Medicine, Public Health Sciences and Obstetrics/Gynecology | Senior Associate Dean for Health Disparity, Miller School of Medicine

#### 2015 Teacher of the Year
- **Diana Lopez, Ph.D.**
  - Member, Sylvester Comprehensive Cancer Center | Professor, Department of Microbiology and Immunology, Miller School of Medicine
2014
Marc Lippman, M.D., MACP, FRCP
Kathleen & Stanley Glaser Professor
Deputy Director, Sylvester Comprehensive Cancer Center | Professor of Medicine

2013
Joseph Rosenblatt, M.D.
Professor of Medicine | Chief, Hematology/Oncology

2012
Izidore S. Lossos, M.D.
Professor of Medicine | Director, Lymphoma Program

2011
Mark D. Pegram, M.D.
Professor of Medicine | Interim Division Chief, Hematology/Oncology | Associate Director for Clinical Research

2010
Eckhard R. Podack, M.D., Ph.D.
Professor of Microbiology and Immunology

2009
William J. Harrington, M.D.
Professor of Medicine | Co-leader, Viral Oncology Program

2008
Joyce M. Slingerland, M.D., FRCP(C), Ph.D.
Professor of Medicine | Director, Braman Family Breast Cancer Institute

2007
Kermit Carraway, Ph.D.
Professor of Cell Biology and Anatomy

2006
Peter Cassileth, M.D.
Professor Emeritus, Division of Hematology/Oncology

2005
Glen Barber, Ph.D.
Professor of Medicine | Associate Director, Basic Science

2004
Diana Lopez, Ph.D.
Professor of Microbiology and Immunology | Program Leader, Tumor Immunology

2003
Antero So, M.D., Ph.D.
Professor of Medicine, Biochemistry and Molecular Biology
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## 2016 ANNUAL SYLVESTER CANCER RESEARCH POSTER SESSION

### TUESDAY, MAY 10, 2016

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BASIC SCIENCE
THE CATALYTIC ACTIVITY OF TET2 IS ESSENTIAL FOR ITS MYELOID MALIGNANCY-SUPPRESSIVE FUNCTION IN HEMATOPOIETIC STEM/PROGENITOR CELLS

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BACKGROUND: Mutations of the TET2 gene frequently occur in spectra of myeloid malignancies, including MDS, MPN, AML, and CMML. The TET2 mutations are mostly heterozygous and also occur in >5% of normal elderly individuals. Tet2-haploinsufficiency (Tet2\(^{-/-}\)) is sufficient to cause CMML in mice. Therefore, TET2 and its pathways represent potential therapeutic targets for intervention. However, it is important to clarify whether the catalytic activity of TET2 is essential for its myeloid malignancy-suppressive function. In addition, it remains to be established at which hematopoietic stem/progenitor cells (HSC/HPCs) developmental stages, TET2-loss is capable of inducing myeloid malignancies.

METHODS: 1) Examine the presence of TET2 mutations in CD34\(^+\), CD33\(^+\), CD19\(^+\) and CD3\(^+\) cell populations purified from myeloid malignancy patients with known TET2 mutations using PCR/direct sequencing. 2) Generate Tet2\(^{fl/fl}\);LysMCre mice (Tet2 inactivation in monocytes/granulocytes/macrophages but not LSK/LK/lymphoid cells) and determine if Tet2\(^{fl/fl}\);LysMCre mice develop myeloid malignancy. 3) Transplant BM Lin- Sca-1- c-Kit\(^+\) (LSK), Lin- Sca-1- c-Kit\(^+\) (LK) or Lin- c-Kit\(^+\) cells from pre-malignant Tet2\(^{-/-}\) mice into WT recipients. 32 weeks after transplantation, recipients were analyzed for their hematological phenotype. 4) Create lentiviral constructs using codon-optimized Tet2 cDNA sequence (Tet2opt) and catalytic domain-inactive mutant Tet2 cDNA sequence (Tet2mu, H1295Y xD1297A) to overexpress FLAG-tagged Tet2opt and Tet2mu (along with GFP) in Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells. 5) Examined the replating potential in vitro and myeloid malignancy-initiating capacity (transplantation assay) in vivo of GFP\(^+\) Tet2\(^{/-}\) HSC/HPCs expressing GFP, Tet2opt or Tet2mu.

RESULTS: 1) TET2 mutations were present in each of the CD34\(^+\), CD33\(^+\) and CD19\(^+\), but not CD3\(^+\), cell populations from all patients, indicating occurrence of TET2 mutations at the common myeloid-B-progenitor level. 2) Aged Tet2\(^{fl/fl}\);Vav1Cre, but not Tet2\(^{fl/fl}\);LysMCre mice exhibited characteristics of CMML or MPN. 5 of the 6 mice receiving Tet2\(^{-/-}\) LSK cells and 3 of the 6 mice receiving Tet2\(^{-/-}\) LK cells, but none of the mice receiving Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells, developed CMML or MPN. These results indicate that Tet2-loss in HSC/HPCs, but not differentiated hematopoietic cells, is capable of inducing myeloid malignancies in vivo. 3) In each round of replating, a higher colony numbers were documented from Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells expressing GFP or Tet2mu compared to WT Lin- c-Kit\(^+\) cells. By contrast, re-introducing Tet2opt into Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells fully rescued their hyper-replating potential. 5) 32 weeks after transplantation, 2/3 of the mice receiving Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells expressing GFP alone or Tet2mu/GFP displayed a CMML phenotype. By contrast, none of the mice receiving Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells expressing Tet2opt/GFP exhibited any sign of abnormal hematopoiesis. These results indicate that re-introducing WT Tet2, but not the catalytic inactive mutant, rescued the myeloid malignancy-initiating capacity by Tet2\(^{-/-}\) Lin- c-Kit\(^+\) cells.

CONCLUSION: Tet2 loss in HSC/HPCs, but not more differentiated cells, is capable of inducing myeloid malignancies. TET2 requires its catalytic activity in HSC/HPCs to exert its myeloid malignancy-suppressive function. Increasing the WT TET2 enzymatic activity to compensate/overcome TET2 haploinsufficiency in HSC/HPCs could represent an effective preventive and therapeutic strategy for individuals with heterozygous TET2 mutations.
PRMT5 REGULATES FETAL ERYTHROPOIESIS BY CONTROLLING THE NUA4 HISTONE ACETYLTRANSFERASE COMPLEX

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BACKGROUND: Profound epigenetic changes accompany erythropoietic cell differentiation. These include changes in DNA methylation and multiple changes in histone post-translational modifications, but also dynamic alternative splicing programs, which all together regulate gene expression during erythropoiesis. We have been studying PRMT5, the major type II arginine methyltransferase in cells, that symmetrically dimethylates histones H2A, H3 and H4, as well as numerous non-histone substrates, including three subunits of the SMN complex (SmB, SmD1 and SmD3), a key component of the RNA splicing machinery.

METHODS: To elucidate the role of PRMT5 in fetal erythropoiesis, we generated a hematopoietic cell specific PRMT5 knockout mouse.

RESULTS: We identified PRMT5 as a master regulator of erythropoiesis. The cell-specific deletion of PRMT5 in fetal liver cells is embryonic lethal, as PRMT5-null embryos have severe anemia and a block in erythropoietic differentiation at the S1 to S2 cell transition. Methyl-seq and RNA-seq studies showed that PRMT5 loss does not globally affect DNA methylation, but leads to upregulation of the p53 signaling pathway. As p53 might be induced by the aberrant splicing triggered by PRMT5 loss, we performed RNA splicing analysis and identified two main groups of genes whose RNA splicing is controlled by PRMT5, RNA processing genes and chromatin modification genes. Notably PRMT5 loss induced the aberrant splicing of Tip60, the enzymatic subunit of the NuA4 histone acetyltransferase complex, which subsequently leads to decreased Tip60-mediated H4 acetylation, global genomic instability and p53-dependent cell death.

CONCLUSION: Thus, we have uncovered a novel functional interaction between PRMT5-dependent RNA splicing and chromatin structure that might regulate fetal erythropoiesis.
ACTIVATION OF HEPATIC INNATE IMMUNE RESPONSES AND INFLAMMATION DURING HIV & HCV CO-INFECTION

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BACKGROUND: Patients with HIV that are co-infected with HCV are at increased risk for rapidly progressive liver disease and subsequently the development of Hepatocellular Carcinoma (HCC). Specifically, HCC develops earlier in co-infected patients and these patients are more symptomatic than those with only HCV infection at diagnosis suggesting that both viruses increase the propensity for malignant transformation. Consequently, HCV coinfection and the associated liver disease is a major health burden for HIV infected persons in the U.S. However, the genetic and cellular based mechanisms underpinning how HCV initiates and subsequently induces liver pathology and why coinfection with HIV results in significantly worse hepatic disease remains to be clarified. In addition, the specific cell types that contribute to these clinical outcomes are unknown. Our overarching hypothesis is that viral infection activates innate immune pathways that subsequently drive inflammation that cause the rapidly progressive liver disease observed in co-infected patients. In this study, we specifically are testing the hypothesis that the robust viral RNA dependent innate immune response that we have characterized, that drives inflammation in HCV infected livers, is augmented with HIV coinfection through activation of viral DNA sensing pathways.

METHODS: Given that infected cell types are of critical importance in the development of HCV-related liver pathology, we utilized primary human hepatocytes (PHHs) and primary kupffer cells (PKCs) as a model system. An established model of HCV infection available for use in cell culture utilizes the JFH1 infectious clone and it is designated HCVcc for virus propagated in cell culture. For models of HIV infection, the HIV-BAL (R5) and HIV-IIIB (X4) strains will be used for this studies. A co-culture model of PHHs and PKCs was also utilized. Upregulated of genes expression such as CXCL10, IL-6, IL-1β and CCL5/Rantes were measured using qPCR analysis or microarray. Proteins expression was detected by utilizing ELISA, flow cytometry, and confocal immunofluorescence microscopy. Data obtained from these primary cells, studied in in-vitro models, will also be used to understand innate immune pathways that are activated in clinical samples from co-infected patients.

RESULTS & CONCLUSION: In this study, we found that HCV and HIV stimulation of these primary liver cells resulted in rapid and robust upregulation of CXCL10, IL-6 and other inflammatory cytokines. Surprisingly, microarray analyses of HIV treated liver cells demonstrated several innate immune pathways were activated by this virus in the liver. Activation of NF-κB -dependent pathways by HCV or HIV were essential for these innate genes upregulation, but viral replication of HIV or HCV was dispensable. We have already established our co-culture models which plated PKCs and PHHs and have tested innate immune responses after infection with HIV. qPCR analysis demonstrated that co-culture of PHHs and PKCs treated with HIV manifest a profound increase in induction of CXCL10 when both cells are present. This result indicates that a crosstalk between PKCs and PHHs impacts the outcome of innate immune responses during viral infection. Overall, our data demonstrate that the robust antiviral response that is observed in HCV infected livers and subsequently drives liver pathology is augmented with HIV/HCV coinfection. It is hoped that understanding the mechanism by which co-infected patients have more severe liver disease will enable the development of targeted therapeutics to abrogate these poor clinical outcomes.
THE EFFECT OF C-TERMINALLY PHOSPHORYLATED p27 ON BREAST CANCER STEM-LIKE CELLS

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BACKGROUND: p27 is a cell cycle regulator that binds and inhibits Cyclin-Cdk5s. In normal quiescent cells, p27 is exclusively nuclear. However, in many PI3K activated cancer cells, p27 is phosphorylated at T157 and T198 by PI3K effector kinases leading to mis-localization of p27 in both cytoplasm and nucleus. Normal epithelial cells express high nuclear p27, but human cancers often have reduced nuclear p27 associated with poor prognosis and p27 can also be observed in the cytoplasm. The present work demonstrated that C-terminally phosphorylation of p27 increases the population of breast cancer cells with stem cell-like properties and explored its mechanisms.

METHODS: To investigate the role of C-terminally phosphorylated p27 (p27pTpT), we established cell cycle defective (CK-), double phosphomimetic p27 T157D/T198D (p27CK-DD) mutant. We introduced this phospho-mimic p27 (p27CK-DD) into breast cancer cell lines and examined the effect on the cancer stem-like cell properties including sphere formation, ALDH1 positivity and embryonic stem cell transcription factors (ES-TFs) expression. In addition, p27 was knocked down in cell lines with high metastatic potential and effects on cell invasion and stem cell properties were evaluated.

RESULTS: p27CK-DD expression increased sphere formation and expression of embryonic stem cell transcription factors (ES-TFs, Nanog, Sox2 and c-Myc) in human breast cancer cells, MCF7 and MDA-MB-231, and in human mammary epithelial cells, MCF12A. In MCF12A cells, p27CK-DD transduction upregulated expression of CD44, a CSC marker in many human cancers, increased ALDH1 activity, and increased cells with surface CD44+CD24^low. MDA-MB-231-4175 cells are metastatic derivatives of the MDA-MB-231 breast cancer line and have more C-terminally phosphorylated p27 compared to parental MDA-MB-231 cells. p27 knockdown in MDA-MB-231-4157 cells reduced stem cell self-renewal ability and ES-TFs (Nanog, Sox2, c-Myc) expression. Notably, we found PI3K activation and p27CK-DD expression both increase Pyk2 activity and elevated Pyk2 activation is required for C-terminally phosphorylated p27-driven stem-like cell properties. Also, C-terminally phosphorylated p27 down-regulated Pyk2 repressor, PTPN12. In vivo work is underway.

CONCLUSION: C-terminally phosphorylated p27 promotes breast cancer stem-like cell properties through PTPN12 down-regulation and Pyk2 activation and upregulation of ES-TFS, driving tumor progression.
KNOCKOUT OF ARGINYLTRANSFERASE LEADS TO WARBURG EFFECT IN MOUSE EMBRYONIC FIBROBLAST CELLS

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BACKGROUND: Protein arginylation by arginyl-transfer RNA protein transferase (Ate1) is a post-translational modification that targets a number of metabolic enzymes. However, the mechanisms and downstream effects of this modification are unknown.

METHODS: Wild type mouse embryonic fibroblast cells (MEF-WT) and Ate1 knockout mouse embryonic fibroblast cells (MEF-KO) were used to measure several key metabolic parameters including glucose uptake, glucose starvation sensitivity, lactate production, and cellular oxygen consumption by established Fluorometric Assay Kit with flow cytometer, enzymatic colorimetric way, and the Hansatech Oxytherm system, separately.

RESULTS: MEF-KO is more sensitive to glucose starvation than MEF-WT, and MEF-KO has significant higher glucose uptake and lactate production than MEF-WT. Simultaneously, the oxygen consumption of MEF-KO is significantly lower than that of MEF-WT.

CONCLUSION: Our data suggest that knockout of Ate1 in MEF shift cellular metabolic pathways from mitochondrial oxidative phosphorylation to aerobic glycolysis, which is the sign of the Warburg effect. Such an effect is likely related to dysfunction of mitochondria.
**P300 acetylates Maml1 to recruit NACK to Notch transcriptional complex**

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Molecular oncology, Surgery, School of Medicine, University of Miami

**BACKGROUND:** The Notch pathway is involved in many different cell processes through regulating Notch target genes. Our lab discovered a novel Notch coactivator, NACK. However, the mechanism how NACK is involved in Notch signaling haven’t been fully explored. P300 was reported to be a Notch coactivator too, but p300 enhance Notch signaling remain unclear. Thus, we hypothesize that p300 acetylates Maml1 to recruit NACK to Notch transcriptional complex.

**METHODS:** DNA pull down assay was performed to isolate the assembled Notch ternary complex from 293T cells through ectopically expressing proteins. We also monitored endogenous Notch transcriptional complex formation by ChIP assay in OE33 cell line, which has high level of Notch signaling. At the same time, qPCR assay of Notch target genes and cell viability assay were performed to detect the change of Notch signaling activity.

**RESULTS:** When p300 was coexpressed, the complex assembled in 293T cell line had more NACK recruitment, while Notch1, Maml1 and CSL remained the same level. In addition, 188K/189K sites on Maml1 were shown to be acetylated by p300 and is important for the recruitment of NACK. In OE33 cell line, p300 knockdown or inhibition blocked the presence of NACK on the HES1 promoter, but didn’t change Notch1 and Maml1’s occupies. At the same, p300 knockdown or inhibition reduced the expression of Notch target genes. Furthermore, DAPT treatments of EAC cell lines were sensitized by p300 inhibition.

**CONCLUSION:** p300 regulates NACK recruitment to Notch transcriptional complex through the acetylation of 188K/189K sites on Maml1, resulting in activation of Notch signaling. This mechanism could provide a novel therapeutic strategy for Notch-dependent tumor.
TUMOR FIBROBLAST TARGETING VIA UPAR RETARGETED MEASLES VIRUS: IN VITRO AND IN VIVO EFFECTS

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University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

BACKGROUND: Tumor stromal cell components, in particular cancer associated fibroblasts, play an important role in cancer progression. Few studies have focused on stromal fibroblast targeting by oncolytic viruses. The urokinase receptor (uPAR) is a clinically and biologically validated target, which is overexpressed in tumor and stromal cells compared to non-cancer tissues. MV-h-uPA and MV-m-uPA are fully retargeted oncolytic measles viruses directed against human and murine uPAR, respectively, which have shown in vitro and in vivo safety and antitumor effects. Species specific retargeted viral vectors allow to dissect the specific effects of the viruses on murine vs. human tissues in xenograft models. Our aim is to characterize the in vitro and in vivo effects of stromal targeting by oncolytic measles virus via uPAR, with a focus on tumor fibroblasts.

METHODS & RESULTS: In vitro, MV-h-uPA and MV-m-uPA preferentially infected and induced cytotoxicity in human cancer associated fibroblasts (CAF 19, CAF 23) as well as murine fibroblasts (3T3), compared to non-tumorigenic fibroblasts. Murine-murine and human-human fibroblast to cancer cell viral transfer via heterofusion was observed after fibroblast infection by species specific MV-uPA, in breast, colon and renal cancer models, while no viral transfer was observed between cells of different species. In vivo, systemic administration of the murine uPA retargeted virus (MV-m-uPA) significantly decreased tumor progression and prolonged survival in a human breast cancer xenograft model (MDA-MD231), where the host stroma expresses murine uPAR (target of MV-m-uPA). Tumor studies revealed induction of apoptosis (TUNEL assay), while no significant effects on cancer cell proliferation was observed. Dual staining for measles virus nucleocapsid proteins and fibroblasts markers demonstrated viral infection of fibroblasts in treated tumors. Gene expression studies using murine as well as human specific arrays were performed to characterize the effects of stromal targeting by the murine retargeted virus on murine stroma as well as the indirect effects on human cancer cells in vivo.

CONCLUSION: Our results show feasibility and antitumor effects of stromal fibroblast targeting by oncolytic measles virus via uPAR and demonstrate that stromal fibroblasts are viable targets for oncolytic virotherapy.
THE SPINDLE ASSEMBLY CHECKPOINT GENE BUB1B IS ESSENTIAL FOR THE BREAST CANCER CELL SURVIVAL

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BACKGROUND: As normal breast epithelium evolves towards malignancy, cells accumulate genomic changes that give them a replicative advantage while at the same time increasing their genomic instability. Increased genomic instability results in accumulation of genomic aberrations that compromise the genomic integrity and, therefore, threaten cell viability, thus putting cancer cells under mitotic stress. As a consequence, cancer cells evolutionarily must adapt themselves to compete with the possible detrimental effects of genomic instability. Finding a balance between the instability that gives them a replicative advantage and the instability that could lead them to mitotic catastrophe is crucial. The mitotic stress caused by genomic instability may require overexpression of certain spindle assembly checkpoint (SAC) genes, which can prevent mitotic catastrophe that would occur if cancer cells undergo mitosis prematurely. Although the full mechanism of action of SAC is yet to be elucidated, Bub1b through its protein BubR1 is an important part of this checkpoint, and inhibits the onset of anaphase until all chromosomes are aligned correctly at the metaphase plate.

METHODS & RESULTS: Our analysis of clinical datasets shows a significant increase in the expression of Bub1b in breast cancer as compared to normal epithelia. Furthermore, Bub1b overexpression correlates with decreased overall survival in patient samples. Our analyses also show a pattern of increasing Bub1b overexpression in more aggressive variants of breast cancer such as triple negative tumors and high-grade tumors, which also tend to be more resistant to current therapies. Expression analyses of breast cancer cell lines reveal that Bub1b overexpression is positively correlated with more aggressive behavior. We postulated that the requirement for Bub1b expression might be a vulnerability of rapidly proliferating cancers; therefore, its inhibition will result in cell death through mitotic catastrophe. Using RNA interference with siRNAs, we reduced Bub1b levels in a variety of breast cancer cells. Our results showed significant decrease in cell viability and clonogenicity in soft agar and increase in apoptosis upon Bub1b knockdown, especially in triple negative breast cancer cell lines. However, the viability of normal breast epithelium cells, MCF12A, was not affected.

CONCLUSION: Our data indicate that Bub1b is a critical player in breast cancer viability, and further investigation of the role of Bub1b in promoting successful proliferation of breast cancer cells with genomic instability could provide a new therapeutic strategy particularly in concert with standard genotoxic treatments such as alkylators, spindle poisons and radiation therapy.
THERAPEUTIC TARGETING OF RAGE INHIBITS BREAST CANCER INVASION AND METASTASIS


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BACKGROUND: The Receptor for Advanced-Glycation End-products (RAGE) is highly expressed in various cancers and is correlated with poor outcome in breast and other cancers. Prior work has implicated RAGE in the metastatic process but few efforts have been made to target this receptor therapeutically or dissect its mechanistic role. Here we identified that RAGE drives invasion and metastasis of breast cancer models through effects on tumor cells and on the tumor microenvironment. Further we tested for the first time the therapeutic potential of RAGE inhibition with novel small molecule drugs to reduce breast cancer progression and metastasis.

METHODS: Using multiple breast cancer cell models we tested the role of RAGE in driving mechanisms of metastasis in vitro and in vivo. These included human MDA-MB-231 and its organotropic lung (4175) and bone (1833) metastatic cell lines, murine 4T1 and their non-metastatic clonal variants (67NR), dissociated primary human tumor cells (DT28), and the AT-3 cell line syngeneic to C57BL6. We tested multiple in vivo models using RAGE overexpression and knockdown in 231 and 4175 cells orthotopically injected into the humanized NSG (NOD-SCID-gamma) xenograft mouse model, 4T-1 in BALBc syngeneic models, and AT-3 cells in C57BL6 wild-type and RAGE knockout mice. Finally, we tested the role of the novel RAGE inhibitor FPS-ZM1 on cancer cell invasion and metastasis in vitro and in vivo.

RESULTS: Highly metastatic variants of the MDA-MB-231 breast cancer line (4175 and 1833) showed increased RAGE compared to parental cells. Moreover, the highly metastatic murine 4T1 breast cancer cells demonstrated higher levels of RAGE than non-metastatic 67NR cells. RAGE overexpression in 231 cells increased levels of EMT transcription factors in a MEK-dependent manner and increased transwell invasion and soft agar colony formation, without affecting proliferation. RAGE overexpression in 231 cells did not change in vivo orthotopic tumor growth compared to 231 controls, but importantly decreased metastasis to lung. We next tested how the loss of RAGE function impacts cell invasion using either FPS-ZM1 or shRNA in 4175, 231 and 4T-1 cells. RAGE shRNA and FPS-ZM1 both decreased transwell invasion and soft agar colony formation, without affecting proliferation, compared to controls. In parental 231 cells, RAGE shRNA knockdown did not affect tumor growth, but dramatically inhibited metastasis to lung and liver. Interestingly, RAGE shRNA knockdown in highly metastatic 4175 cells in vivo decreased orthotopic tumor growth, reduced tumor angiogenesis and recruitment of inflammatory cells, and dramatically decreased metastasis to lung and liver in a time and sized matched manner compared to scrambled controls. Finally, in preclinical studies, treatment of orthotopic 4175 tumors in vivo with FPS-ZM1 (1mg/kg) inhibited primary tumor growth and prevented metastasis to lung and liver compared to vehicle treatment.

CONCLUSION: These powerful and novel data clearly demonstrate a role for RAGE in breast cancer progression and metastasis. Furthermore, our data from drug inhibitor studies highlights RAGE as a novel therapeutic approach for breast and other metastatic cancers.
RESISTANCE TO MEK INHIBITION IN PANCREATIC CANCER IS ASSOCIATED WITH AMPHIREGULIN MEDIATED EGFR-STAT3 ACTIVATION


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BACKGROUND: Targeting KRAS has remained an elusive goal. Therefore, efforts have focused on targeting downstream effectors of RAS. The clinical efficacy of MEK inhibitors in other malignancies confirms that targeting the MAPK pathway has therapeutic potential. Unfortunately, clinical trials of MAPK-directed therapies have been unsuccessful in PDAC. Here, we report a novel mechanism of resistance to MAPK-directed therapies, which is associated with amphiregulin (AREG)-mediated activation of EGFR-STAT3 signaling.

METHODS: The effects of MEK inhibition on the phosphorylation of multiple signaling proteins and EGF family ligands was assessed. AREG release was measured in the conditioned media of PDAC cells treated with MEK, EGFR, STAT3, and/or TACE inhibitors and TACE siRNA knock down cells treated with MEK, EGFR, or STAT3 inhibitors. Tumorigenicity assays were performed with human PDAC cells, xenografts and patient derived xenografts (PDXs) treated with inhibitors for TACE, MEK, EGFR and STAT3 in combinations. PKT mice (Ptf1a\textsuperscript{cre+};LSL-Kras\textsuperscript{G12D};Tgfb\textsuperscript{r2fl/fl}) were treated with AZD6244 and AZD1480 and assessed for overall survival (OS). Tissues from the xenografts and PKT mice were analyzed for cell proliferation and apoptosis markers.

RESULTS: Our results show that MAPK inhibition leads to activation of TACE and EGFR and subsequent activation of STAT3 signaling. Combined inhibition of MEK/STAT3 or MEK/EGFR resulted in sustained blockade of MEK, EGFR, and STAT3 signaling, and decreased tumorigenicity. Overall survival in PKT mice was extended to a median of 85 days with combined MEK and STAT3 inhibition vs. 52 days for vehicle treated mice (p < 0.001). AREG release was significantly reduced with combined MEK/STAT3 inhibition. Evaluation of TACE activation and AREG shedding/release in response to MEK inhibition demonstrated that resistance to MEK inhibition in PDAC is mediated by reactivation of the STAT3 pathway, which is strongly influenced by increased AREG production.

CONCLUSION: Our study provides insights into the molecular mechanisms that help explain the therapeutic resistance of PDAC to MEK pathway inhibition.
EVALUATING THE ANTI-TUMOR ACTIVITY OF MUTANT-IDH1 SPECIFIC INHIBITOR IN HUMAN CHONDROSARCOMA CELLS

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BACKGROUND: Chondrosarcomas are malignant bone tumors that produce cartilaginous matrix. Mutations in isocitrate dehydrogenase enzymes (IDH1/2) were recently described in several cancers including chondrosarcomas. The IDH1 inhibitor AGI-5198 abrogates the ability of mutant IDH1 to produce the oncometabolite D-2 hydroxyglutarate (D-2HG) in gliomas. We sought to determine if treatment with AGI-5198 would similarly inhibit tumorigenic activity and D-2HG production in IDH-mutant chondrosarcoma cells.

METHODS: Two human chondrosarcoma cell lines, JJ012 and HT1080 with endogenous IDH1 mutations and a human chondrocyte cell line C28 with wild type IDH were employed in our study. Mutation analysis of IDH1/2 was performed by PCR-based DNA sequencing, and D-2HG was detected using tandem mass spectrometry.

RESULTS: We confirmed that JJ012 and HT1080 harbor IDH1 R132G and R132C mutation, respectively, while C28 had no mutation. D-2HG was detectable in cell pellets and media of JJ012 and HT1080 cells, as well as plasma and urine from an IDH-mutant chondrosarcoma patient, which decreased after tumor resection. AGI-5198 treatment decreased D-2HG levels in JJ012 and HT1080 cells in a dose-dependent manner, and dramatically inhibited colony formation and migration, interrupted cell cycling, and induced apoptosis.

CONCLUSION: Our study demonstrates anti-tumor activity of an IDH1 inhibitor in IDH1-mutant chondrosarcoma cell lines, and suggests that D-2HG is a potential biomarker for IDH mutations in chondrosarcoma cells. Thus, clinical trials of IDH inhibitors are warranted for patients with IDH-mutant chondrosarcomas.
ASSOCIATION OF RADIOMICS AND METABOLIC TUMOR VOLUMES IN RADIATION TREATMENT OF Glioblastoma Multiforme

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BACKGROUND: High-throughput extraction of imaging and metabolomic quantitative features from MRI and MR Spectroscopy Imaging (MRSI) of Glioblastoma Multiforme (GBM) results in tens of variables per patient. In radiotherapy (RT) of GBM the relevant metabolic tumor volumes (MTVs) are related to aberrant levels of with N-Acetylaspartate (NAA) and Choline (Cho). The corresponding Clinical Target Volumes (CTVs) for RT are based on Contrast-Enhancing T1-weighted (T1w) and T2-weighted/FLAIR MRI. The objective is to build a framework for investigation of the associations between imaging, CTVs, and MTVs features for better understanding of the underlying information in the CTVs and dependencies between these volumes.

METHODS: Necrotic portions, enhancing lesion and edema were manually contoured on T1w/T2w images for 17 GBM patients. CTVs and MTVs for NAA (MTV_{NAA}) and Cho (MTV_{Cho}) were constructed. Imaging and metabolic features, related to size, shape, and signal intensities of the volumes were extracted. Tumors were also scored categorically for ten semantic imaging traits by a neuroradiologist. All features were investigated for redundancy. Two-way correlations between imaging and CTVs and MTVs features were visualized as heat maps. Associations between MTV_{NAA} and MTV_{Cho} and imaging features were studied using Spearman correlation.

RESULTS: 48 imaging features were extracted per patient. Half of the imaging traits were replaced with automatically extracted continuous variables. 20 features were extracted from CTVs and MTVs. A series of semantic imaging traits were replaced with automatically extracted continuous variables. There were a high number (43) of significant correlations of imaging measures with CTVs/MTV_{NAA} while very few (10) with CTVs/MTV_{Cho}.

CONCLUSION: A framework for investigation of co-dependencies between MRI and MRSI radiomic features and CTVs/MTVs has been established. MTV_{NAA} was found to be closely associated with MRI volumes, while very few imaging features were related to MTV_{Cho}, indicating that Choline provides independent to imaging information.
MECHANISM AND DISRUPTION OF ANDROGEN RECEPTOR VARIANT ENHANCEMENT BY IS CO-ACTIVATOR VAV3: A NOVEL TARGETED APPROACH FOR PROSTATE CANCER

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BACKGROUND: Prostate cancer (PC) is the second most common cancer in men (1), and androgen deprivation therapy, the gold standard of treatment for non-organ confined prostate cancer, provides palliative relief with tumor regression and falling levels of prostate specific antigen. However, virtually all patients relapse within 3 years (2,3). At this stage, the disease is termed castration resistant prostate cancer (CRPC). Multiple mechanisms allows the progression of CRPC, and one of them is through the increased expression of androgen receptor splice variants (ARv), which are forms of AR lacking the carboxy-terminus and ligand binding domain (LBD), but that retain the transactivating N terminal domain (NTD) (4). As such, many are constitutively active transcription factors that confer in vitro and in vivo castration resistance (5,6). CRPC is a rapidly progressing disease state for which there is no cure. AR and ARVs signaling is augmented by a novel co-activator: Vav3 (7,8), a guanine nucleotide exchange factor (GEF), whose levels increase upon progression to castration resistance in cell lines, mouse, and human specimens (7, 9 -11). Vav3 enhances androgen-mediated AR N-C interaction (8, 12); however, ARVs observed in CRPC lack the C-terminus.

METHODS: For this study we used mutational and biochemical assays in vitro, together with computational analysis of PC patient samples from independent datasets.

RESULTS: We demonstrated that Vav3 enhanced AR-V7 activity (the most commonly expressed ARv in patient samples) by mechanisms distinct from co-activation of full length AR (not dependent on N-C interaction). Peptide expression of the Vav3 region that binds AR-V7 disrupted the AR-V7:Vav3 specific interaction, which decreased AR-V7 activity, but not full length AR activity. Furthermore, disruption of AR-V7:Vav3 interaction led to decreased AR-V7 nuclear translocation and proliferation of CRPC lines expressing both Vav3 and AR-V7. Finally, our computational analysis on PC patient samples shows that all the metastatic samples that exhibited elevated levels of AR-V7 also expressed significant expression of Vav3, suggesting that the AR-V7:Vav3 interaction indeed occurs in clinical samples.

CONCLUSION: These data, showing physical and functional interactions between Vav3, a unique AR co-activator, and ARVs, as well as its clinical relevance, demonstrate the potential therapeutic utility of inhibiting constitutive active AR signaling, and thereby CRPC progression, through disruption of ARVs:Vav3 interactions as a novel targeted approach.
EVALUATING THE ANTI-TUMOR ACTIVITY OF MUTANT-IDH1 SPECIFIC INHIBITOR IN HUMAN CHONDROSARCOMA CELLS

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BACKGROUND: The increasing incidence of pancreatic cancer is associated with a rising prevalence of obesity, a documented risk factor for the disease. Obesity harbors a systemic chronic inflammatory disorder characterized by increased production and secretion of pro-inflammatory adipokines Leptin, TNF-α, and IL-6; while exhibiting a decrease in the anti-inflammatory adipokine: adiponectin. Dysregulation of these factors is thought to be a key mechanism of obesity associated cancers, contributing to increased activation of mitogenic pathways including PI3K and MAPK. Adiponectin represents an important negative regulator of Leptin, TNF-α and IL-6. We previously demonstrated that adiponectin inhibits pancreatic cancer proliferation and tumor growth, however, the molecular mechanisms by which it regulates these processes are unknown. We hypothesize that Adiponectin Receptor (AdipoR) agonists elicit anti-tumor effects through suppression of RAS-MAPK mediated pathways in pancreatic cancer progression.

METHODS: The anti-tumor effects of AdipoRon, a small molecule agonist of the AdipoR, were assessed in vitro on human and murine pancreatic cancer cell lines. Cells were treated with AdipoRon in a dose-dependent manner and then assayed for cellular proliferation, apoptosis, colony formation and anchorage-independent growth. The effect of AdipoRon on activation of key RAS-MAPK signaling regulators was investigated by immunoblot analysis. To determine whether AdipoRon could inhibit the effects of obesity associated pro-tumorigenic cytokines, human and mouse pancreatic cancer cells were exposed to recombinant Leptin or recombinant IL-6. To determine whether AdipoRon could inhibit tumor growth in vivo, mice were orthotopically injected in the pancreas with the murine KrasG12D mutant P-4313 cell line. Tumors were allowed to establish for two weeks and treated with either vehicle or AdipoRon. Tumor size and number of Ki67 positive cells were assessed.

RESULTS: Compared to vehicle treatment, in vitro assessment confirmed that AdipoRon was highly effective at inhibiting cell proliferation, increasing apoptosis and preventing colony formation for all pancreatic cell lines tested. Anchorage independent growth was drastically reduced for both Panc1 and MiaPaca-2 cell lines in the presence of AdipoRon. Treatment of both murine and human pancreatic cancer cell lines with AdipoRon caused a significant dose dependent decrease in pSTAT3, pERK1, and pERK2 with a simultaneous increase in pAMPK. Importantly, AdipoRon completely antagonized the stimulatory effects of Leptin or recombinant IL-6 on the activation of pSTAT3. Administration of AdipoRon to P-4313 orthotopic pancreatic tumor bearing mice resulted in four fold decrease in tumor size and a 50% reduction in tumor cell proliferation.

CONCLUSION: AdipoRon, an AR agonist, suppresses KRAS signaling mediators ERK and STAT3 while simultaneously increasing AMPK resulting in inhibition of pancreatic cancer proliferation and tumor growth. Targeting of adiponectin receptors can provide a viable therapeutic strategy for the treatment of pancreatic cancer.
C-TERM INALLY PHOSPHORYLATED P27 DRIVES EMT AND METASTASIS BY SCAFFOLDING A TRANSCRIPTIONAL COMPLEX WITH C-JUN TO DRIVE TGF-β2

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BACKGROUND: In normal cells, p27 restrains the cell cycle by inhibiting cyclin-CDKs. In human cancers, p27 is deregulated by PI3K-dependent phosphorylations at T157 or T198 that impede p27 import leading to p27 localization in both the cytoplasm and nucleus. We and others have identified an oncogenic role for p27 in mediating motility, invasion and metastasis resulting from these C-terminal phosphorylations. The present work investigated mechanisms whereby p27 contributes to EMT and metastasis.

METHODS: MDA-MB-231-1833 is a highly PI3K-activated metastatic derivative of the MDA-MB-231 breast cancer line that exhibits high levels of C-terminally phosphorylated p27. The gene expression profiles of parental low metastatic MDA-MB-231 and highly metastatic MDA-MB-231-1833 were compared to the metastatic and EMT gene signatures using gene expression microarrays. Thereafter, we examined the effects of p27 knockdown on genes that were changed during the transition from MDA-MB-231 to MDA-MB-231-1833. In addition, to further investigate the mechanism in which p27pT157pT198 promotes EMT and metastasis, cell cycle defective (CK1), double phosphomimetic p27 T157D/T198D (p27CK-DD) mutant were transduced into less metastatic MDA-MB-231 or the non-transformed cell line, MCF-12A.

RESULTS: p27 knockdown in highly metastatic MDA-MB-231-1833 cells induced re-expression of metastasis-suppressor genes, and reverted an EMT gene signature. p27 knockdown in PI3K-activated, metastatic lines reduced expression of EMT drivers including SNAI1, SNAI2, ZEB2, and TGF-β2, but not TGF-β1. Transduction of a cell cycle defective (CK1), double phosphomimetic p27CK-DD, into less metastatic or non-transformed cell lines increased SNAI1, SNAI2, ZEB2, and TGF-β2 expression. Notably, TGF-β2 knockout using CRISPR/Cas9 reduced invasion and reverted EMT with downregulation of EMT drivers in p27CK-DD transduced cells suggesting p27pT157pT198 promotes EMT and metastasis through TGF-β2. p27CK-DD over-expression in human mammary epithelial cells increased c-Jun activity and c-Jun was decreased by p27 knockdown in MDA-MB-231-1833. In silico analysis revealed AP-1 binding sites at upstream of the TGF-β2 promoter. IP blotting showed p27pT157pT198 binds JNK/c-Jun in the cytoplasm but binds only c-Jun in the nuclear fractions. ChIP analysis showed p27 co-localized with c-Jun at an AP-1 motif -15KB upstream of the TGF-β2 transcriptional start site to induce TGF-β2. Furthermore, p27CK-DD transduced cells show greater p27/c-Jun binding to the upstream enhancer site in TGF-β2 promoter region compared to control cells in Quantitative ChIP assay, suggesting that C-terminal p27 phosphorylation may enhance c-Jun-driven TGF-β2 gene induction via increasing its binding to the upstream of TGF-β2 promoter.

CONCLUSION: Taken together these data suggest that PI3K-driven p27pT157pT198 promotes EMT and metastasis through coactivation of c-Jun to induce expression of the TGF-β2 gene leading to EMT-TF activation and metastatic tumor progression. c-Jun is also known to regulate transformation and stem cell self-renewal. Present work opens a novel paradigm that p27 may not only serve as a CDK inhibitor, but also play a novel role as a transcriptional co-activator with c-Jun and potentially other key transcriptional drivers to drive programs of EMT, metastasis and stemness.
PDGFRα DEFINES A KAPOSI’S SARCOMA PROGENITOR CELL POPULATION AMONG MESENCHYMAL STEM CELLS

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BACKGROUND: Kaposi’s sarcoma (KS), an AIDS-defining cancer caused by the KS herpesvirus (KSHV), is a vascular sarcoma characterized by intense angiogenesis and spindle cell proliferation. Key pending questions on KS are its cellular ontology and the molecular mechanisms of viral oncogenesis. The initial KSHV target cells could be precursor cells, and KS like spindle endothelial precursor cells are present in the blood of KS patients. The origin of this spindle cells remains enigmatic, because they express markers of multiple cellular lineages, including endothelial, monocyctic, and smooth muscle, suggesting that a circulating hematopoietic progenitor cell (HSC) could give rise to KS spindle cells, especially endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSC). Since we identified PDGFRα as a predominant oncogenic signaling in KS and that PDGFRα is a key marker of mesenchymal stem cells, we tested the infection of PDGFRα+ve and PDGFRα-ve mouse mesenchymal stem cells as possible KS cellular progenitors.

RESULTS: We found KSHV and PDGFRα co-regulation and activation in PDGFRα +ve cells. We also found an upregulation of endothelial and angiogenic host gene expression that correlates with a major upregulation of the oncogenic lytic program of KSHV infection when this cells are grown in a media used to isolate and differentiate Endothelial Progenitor Cells (EPC), this media is supposed to reproduce an angio/vasculogenic environment (EPC media). To study correlations of host and viral gene expression with oncogenicity we carried out a massive NGS approach by RNAseq and our preliminary conclusions regarding the mechanisms of oncogenicity in PDGFRA+ve KSHV EPC media are that these particular growth conditions and lineage are conducive to a de-repressed KSHV epigenome, which allows for expression of oncogenic KSHV genes. These preliminary conclusions are supported by experiments with two opposite epigenetic regulators. On one hand, treatment with an HDAC inhibitor such as SAHA/ Vorinostat did not showed enhanced KSHV lytic gene expression for infected cells grown in EPC media. Conversely treatment with the differentiating agent All Trans Retinoic acid (ATRA) led to repression of KSHV in EPC media grown cells to levels observed for cells grown in MSC media. When we tested the tumorigenesis of all the KSHV infected and uninfected MSCs we found that both the growth in EPC media and PDGFRA+ve lineage favored tumorigenesis in all injected mice. More importantly, the tumors exhibited robust expression of vGCP and displayed activated PDGFRα signaling which co-localized with KSHV-LANA.

CONCLUSION: This work identify PDGFRα+ve mesenchymal stem cells as KS cellular progenitors in which infection with KSHV has oncogenic consequences when this stem cells are direct to an endothelial lineage. We proposed that viral oncogenes mediated growth factors secretion can recruit circulating KS progenitors (PDGFRα+ve) that can be infected de novo and transformed by KSHV. This system is a very robust platform to identify KSHV oncogenesis-pathways and their relationship with cellular lineages and extracellular growth environments. Moreover it opens the door for un-restricted use of GEM mice and viral genetic systems.
ROLE OF REACTIVE OXYGEN SPECIES SCAVENGER GLUTATHIONE S-TRANSFERASE ALPHA 2 IN EARLY OVARIAN CANCER

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BACKGROUND: High-grade serous carcinoma (HGSC) accounts for majority of ovarian cancer death and is usually diagnosed when the cancer has spread throughout the abdomen. As a result this disease is difficult to treat and 60-70% of patients succumb within 5 years of initial diagnosis. Despite the multiple options available for treatment of disease recurrence, there are no effective screening methods for early detection. Recent evidence has implicated the fallopian tube epithelium (FTE) as the major site of origin for HGSC, neoplastic lesions (STIC), occurs most frequently at the distal fimbriated end of the FTE. In 3 previous reports, we have demonstrated that the FTE of BRCA1 mutation carriers are at a higher genetic risk for HGSC and have altered signaling pathways compared to controls. Ovarian production of reactive oxygen species (ROS) is released after the luteinizing hormone surge to induce ovulation; similarly ROS can form via retrograde menstruation and Fenton’s reaction. ROS have been implicated in serous carcinogenesis. High ROS levels are likely a source of ‘mutagens’, which cause DNA damage in the FTE and possibly contribute to mutations and may compromise ROS scavenging enzymes meant to protect cells from DNA damage. The combination of mutations and alteration of these scavenger enzymes can provide an escape or by-pass through cell-cycle checkpoints to allow for additional cancer promoting mutations, amplifications or deletions in the genome which may lead to carcinogenesis. We have shown that Glutathione S-transferase alpha 2 is upregulated in the normal fimbria (high-risk epithelia prone to transformation) compared to the ampulla (low-risk region), is predominantly expressed in ciliated cells and is lost in HGSC. The objective of this study is to investigate the role of antioxidant gene Glutathione S-transferase A2 (GSTA2) function in normal FTE and in a HGSC tumor progression model.

METHODS: Consented patients fallopian tubes were obtained from women undergoing bilateral salpingooophorectomy (BSO) in the University of Toronto Health Network, Jackson Memorial hospital and the University of Miami hospital. 5µm sections of the FFPE specimen of the profiled cases were stained for proliferation, epithelia and scavenger markers (Ki67, p53, Vimentin, FoxJ1, Pax8, CK7, CK18, GSTA2 and ME1). For cell culture experiments, fallopian tubes were diced and incubated in dissociation media (MEM containing 1.4mg/ml Pronase and 0.1mg/ml DNase) for 48 hours. After 48 hours cells were plated in Ham’s F12 media supplemented with 2% Ultra G and 1% PS on transwell filters to maintain a polarized culture. To develop a HGSC progression FTE cells were infected with CCNE, shp53, p53-R175H, p53-R249S and p53-R273H lentivirus to recapitulate the earliest genomic events observed in ovarian cancer. Cell morphology, death, proliferation, GSTA2 localization and oxidative DNA damage were examined.

RESULTS: There were more GSTA2 positive cells in the fimbria compared to the ampulla. Ciliated cells predominantly express GSTA2. There was a decrease in expression of GSTA2 in FTE cells which over-expressed p53. In vitro data suggested that there was a decrease in ciliogenesis of FTE cells that overexpressed mutant p53. GSTA2 localized to the nucleus of non-ciliated FTE cells, and other cytosolic organelles.

CONCLUSION: Ciliated cells uniquely express anti-oxidant enzymes (GSTA2) which incidentally is more abundant in the fimbria than the ampulla. GSTA2 expression and ciliogenesis is affected by p53 in FTE. Probed further, this insight will help us to better understand the pre-neoplastic responses to ROS stresses in the FTE and how these changes contribute to the pathogenesis of ovarian cancer.
TELOMERE-INDEPENDENT RAP1 IS A NOVEL REGULATOR OF ACTIVATION-INDUCED DEAMINASE EXPRESSION IN B CELLS.

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BACKGROUND: Immunoglobulin (Ig) class switch recombination (CSR) is an essential mechanism for the diversification of humoral immune response through efficient generation of antibody isotypes that mediate elimination of pathogens. CSR is a programmed deletional recombination event between DNA double strand breaks in the Ig heavy chain gene locus (Igh). These DNA breaks are initiated by the mutagenic enzyme, activation-induced cytidine deaminase (AID), which preferentially deaminates the Igh genes but also exhibits ‘off-target’ activity in non-Ig genes including proto-oncogenes. Undesired byproducts of AID function are oncogenic mutations that are a hallmark of B cell malignancies. AID expression levels seem to correlate with the extent of its physiological and pathological functions.

METHODS: Wild-type and RAP1-deficient mouse models as well as a mouse lymphoma cell line were used to induce cytokine-dependent class switch recombination in ex-vivo and in vitro assays. Class switch recombination efficiency, cell proliferation, AID and RAP1 expression and NF-κb activation were evaluated following standard biochemical and cell biology methods.

RESULTS: In this study, we identify the telomeric protein RAP1 as a novel factor involved in the NF-κb-dependent expression of AID in B cells. Consequently, RAP1 deficiency in mouse B cells results in a reduction of NF-κb activation as well as in a decrease in AID expression. Decrease of AID expression in RAP1-deficient B cells induces a decrease in antibody gene diversification efficiency and AID-dependent off-target mutation.

CONCLUSION: Our results identify a novel role for RAP1 through which it regulates an important protein involved in the antibody response to antigens, independent of its ability to regulate telomere function. Furthermore, RAP1 inhibition represents a new pharmacological target to down-regulate AID expression and activity, which could be relevant for therapy of some lymphomas and leukemias.
TALIN PLAYS AN IMPORTANT ROLE IN CELL-CELL INTERACTIONS

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BACKGROUND: Talin is a large scaffolding molecule that plays a major role in integrin dependent cell-matrix adhesion. Recently a role for the C-terminal region of talin (the VAD fragment) in cell-cell attachment has been demonstrated but its molecular mechanism has not been described in detail.

RESULTS: Here, we identified a small region of the VAD fragment required for its localization to cadherin mediated cell-cell junctions and also found that its localization to cell-cell junctions is independent of its actin binding properties. Key residues required for this localization were also identified. To identify the binding partner of the VAD fragment at cell-cell junctions we utilized GFP-pulldown and SILAC techniques and found that it interacts with α-catenin, an important component of cadherin mediated cell-cell junction. Several other novel binding partners were also found.

CONCLUSION: Based on our data, we proposed that the VAD-fragment of talin stabilized and/or stimulated the cell-cell junction by interacting with α and β catenin.
TARGETING THE IMMUNE-MICROENVIRONMENT WITH COMBINED INHIBITION OF MEK AND STAT3 IN A MOUSE MODEL OF PANCREATIC CANCER

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BACKGROUND: Activating KRAS mutations are commonly found in PDAC and lead to constitutive downstream activation of MEK, which results in uncontrolled proliferation. We have previously shown that MEK inhibition results in activation of STAT3 signaling which confers drug resistance and continued cancer cell growth while combined STAT3 and MEK inhibition overcomes this resistance. Since STAT3 is a critical mediator of cytokine signaling and MEK is a mediator of cytokine production, we sought to determine the effects of MEK and STAT3 inhibition on the immune tumor microenvironment (TME). Tumor infiltrating immune cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and macrophages support tumor growth. We hypothesized that combined MEK and STAT3 inhibition downregulates the suppressive immune infiltrates and promotes an anti-tumor microenvironment.

METHODS: To understand the effect of MEK and/or STAT3 inhibition of PDAC cells, three dimensional spheroid cultures of PDAC cells (MiaPaCa-2, Panc-1, BxPC3) were prepared. Spheroid cultures were treated with inhibitors to MEK (AZD6244) and/or STAT3 (AZD1480) for 10 days and then quantified for size and metabolic activity. To determine in vivo effects, Ptf1a<sup>cre</sup>;<LSL-Kras<sup>G12D</sup>;Tgfbr2<sup>fl/fl</sup> (PKT) mice were treated with vehicle, MEK inhibitor, STAT3 inhibitor, or combination for 2 weeks. Post-treated pancreatic tissue was extracted, weighed, and examined using immunohistological and enzymatic analyses. Alternately, cells were isolated from the pancreas and spleen, and subsequently labeled for markers to macrophages, myeloid cells, and T cells and then analyzed with flow cytometry.

RESULTS: MEK inhibition resulted in reduced spheroid size and metabolic activity; however, combination MEK/STAT3 treatment led to a significant decrease in spheroid size. In PKT mice, treatment with combined inhibitors for MEK and STAT3 resulted in reduced tumor formation compared to either agent alone. Histological analysis showed that combination treatment maintained pancreatic integrity, with an increased percentage of normal acini, reduced CK-19 staining, reduced collagen deposition, and minimal alcian blue stain. Analysis of the tumor immune infiltrates revealed a significant reduction in the immunosuppressive/tumor promoting myeloid derived suppressor cell (MDSC) population (CD45<sup>+</sup>CD11b<sup>+</sup>Ly6g<sup>+</sup>Ly6c<sup>+</sup>) and regulatory T cell population (CD45<sup>+</sup>CD3e<sup>+</sup>CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>) in the pancreas of mice treated with combined MEK/STAT3 inhibition compared to control mice. Alternately, combined MEK/STAT3 inhibition promoted an increased neutrophil population (CD11b<sup>+</sup>Ly6c<sup>+</sup>Ly6g<sup>+</sup>), but a decreased inflammatory M1 macrophage population (CD45<sup>+</sup>F4/80<sup>+</sup>CD80<sup>+</sup>CD86<sup>+</sup>).

CONCLUSION: Combined MEK/STAT3 inhibition downregulates the tumor promoting immune infiltrates resulting in dramatically reduced tumor burden and enhanced normal pancreatic tissue in a highly aggressive mouse model of pancreatic cancer.
REDOX-PROTECTIVE MECHANISMS AS A THERAPEUTIC ACHILLES HEEL IN CASTRATION-RESISTANT PROSTATE CANCER


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Androgen deprivation therapy (ADT) initially suppresses prostate cancer (PC) progression. However androgen-refractory PC cells inevitably emerge from the androgen-responsive tumor, leading to incurable disease. It is known ADT induces predominantly proliferation arrest in responsive tumor cells and that castration-resistant prostate cancer (CRPC) variants arise clonally from the nonproliferating tumor. We recently demonstrated the AD-induced proliferative defect is a form of cellular senescence, which inhibits the p53/Bax cell death pathway and promotes outgrowth of CRPC subpopulations. Thus identifying combinatorial treatments able to induce acute and pervasive cell death instead of proliferation arrest in response to ADT is likely to both shorten ADT duration and make it more effective by eliminating the tumor cells that give rise to incurable CRPC. Here we investigate whether enhanced oxidative stress can synergize with AD to subvert the initial tumor suppressor response from cell senescence to cell death in AD-responsive PC cells and re-sensitize established CRPC to AD. Our results suggest induction of oxidative stress results in maintenance of androgen receptor (AR) and p53 expression even under AD, leading to cell death and efficient tumor suppression. Thus compromising redox-protective pathways such as TRX1 in conjunction with ADT could be a potent mechanism to prevent emergence and/or limit progression of androgen-refractory PC.
WHOLE EXOME SEQUENCING OF LACRIMAL GLAND ADENOID CYSTIC CARCINOMA

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BACKGROUND: Lacrimal gland adenoid cystic carcinoma (LGACC) is a rare form of orbital cancer. LGACC is difficult to control locally and the 5-year survival rate is ~50% regardless of the form of local treatment. The genetics of LGACC remains largely unclear. Earlier works suggest allelic deletion at loci including chromosome 1p36 locus. Recently, mutations in genes KRAS, NRAS and MET are reported in LGACC using a sequenome genotyping method.

METHODS: To fill in the knowledge gap in the mutation profile of LGACC, we examined 14 LGACC samples using whole exome sequencing (exome-seq). DNA was extracted from 2 fresh-frozen samples and 12 FFPE samples. Whole exome DNA was captured using the SureSelect XT kit and processed by a HiSeq 2000 sequencer.

RESULTS: The mutation profile of LGACC is complicated. Of the 25 most frequent oncogenes in all types of cancer, only 9 genes including TP53, KRAS and BRAF were found without any mutations. The mutation profile of LGACC is similar to the published profile of head and neck ACC. The most shared and functional plausible mutations were accumulated in the notch pathways, especially in the genes NOTCH1, NOTCH2 and notch negative regulator SPEN. The mutations in NOTCH genes are mainly located in the intracellular domain and predicted to cause hyperactivation of notch signaling. The nonsense mutation in SPEN is likely loss of function. Of the 14 LGACC samples, only one sample does not carry any mutations in notch pathway genes.

CONCLUSION: Overall, this is the first report of LGACC mutation profile and notch pathway could be a potential therapeutic target for LGACC.
**P16ink4a CONTROLS MAMMARY EPITHELIAL CELL AGING AND PROTECTS BRCA1 MUTANT CELLS FROM TUMORIGENESIS**

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**BACKGROUND:** Aging is a major risk factor of cancer. One of the major causes of aging is senescence, a cellular response that prevents the proliferation of genomically damaged but otherwise replication-competent somatic cells at risk for neoplastic transformation. Control of the G1 phase of the cell cycle is intrinsically linked with the maintenance of the senescent state, and is primarily controlled by the RB pathway. Alterations of the RB pathway consisting of INK4-Cyclin/CDK-RB are among the most frequent events in human breast cancers, including loss-of-function mutations of p16ink4a (p16 hereafter). p16 is a member of the INK4 family of cell cycle inhibitors, which exclusively binds to and inhibits CDK4/6 preventing cell cycle progression from G1 to S phase. Unlike other INK4 genes, p16 is barely detected during early development and is induced during aging. p16 is inactivated in ~30% of human breast cancers and ~60% of breast cancer cell lines. Separately, BRCA1 is a tumor suppressor associated with 50% of all familial breast cancers. However, mutation of BRCA1 alone rarely results in tumor formation, but instead induces premature senescence in mice. Importantly, Rb is a major target for genomic disruption in breast cancers arising in Brca1 mutation carriers, and dysfunction of the p16-Rb pathway was commonly observed in BRCA1-deficient triple-negative breast cancers. How BRCA1 and p16 control mammary epithelial cell aging and tumorigenesis is largely unknown.

**METHODS:** Utilizing mice obtained from our collaborators or generated by ourselves we study how p16 controls mammary aging and mammary tumorigenesis, and whether Brca1-insufficiency induces p16 leading to premature senescence and if loss of p16 rescues the cell growth defects of Brca1-mutant mice resulting in tumorigenesis.

**RESULTS:** We found that during aging mammary stem cell function declined, which was attenuated by deletion of p16. Disruption of Brca1, in the mammary epithelium resulted in premature senescence with increased p16 expression and a decline of stem cell function that was also rescued by p16 loss. We found that p16 loss transformed Brca1-deficient mammary epithelial cells and induced mammary tumors, though p16 loss alone was not sufficient to induce mammary tumorigenesis. We demonstrated that loss of both p16 and Brca1 induced basal-like mammary tumors with the induction of EMT and an enrichment of cancer stem cells (CSCs).

**CONCLUSION:** This data is consistent with our hypothesis that p16 controls mammary aging and protects mammary cells from transformation by inducing premature senescence.
NOTCH1 SIGNALING DETERMINES MELANOMA-REGULATING ROLE OF TUMOR STROMAL FIBROBLASTS

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BACKGROUND: Tumor stromal fibroblasts are crucial in regulating tumor growth, invasion and metastasis, yet the molecular mechanisms that determine the tumor regulatory role of stromal fibroblasts remains unknown. Here, we uncover the Notch1 signaling pathway as a molecular determinant that controls the tumor regulatory role of tumor stromal fibroblasts in melanoma growth and invasion.

METHODS: Murine melanoma cells B16-F10, stably transduced with Luciferase 2 (Luc2)/lentivirus, were xenografted on the skin of two new mouse lines: the Gain-Of-Function of Notch1 (GOFNotch1: Fsp1.Cre+/–;ROSA26S-N1ICre/+) and Loss-Of-Function of Notch1 (LOFNotch1: Fsp1.Cre+/–;Notch1LoxP/LoxP+/-), respectively. GOFctrl (FSP1.Cre+/–;ROSA26S-N1ICre/+) and LOFctrl (FSP1.Cre+/–; Notch1LoxP/LoxP+/-) mice were used as control. Tumor growth was measured based on tumor weight and melanoma local invasion were examined by H&E staining of resected tumor tissue.

RESULTS: Using a mouse melanoma model in which exogenous melanoma cells were grafted on the skin of two lines of mice where the genetic activation or inactivation of Notch1 signaling specifically occurs in natural host stromal fibroblasts, we demonstrated that Notch1 pathway activity could determine the tumor-promoting or tumor-suppressing phenotype in tumor stromal fibroblasts. Tumor stromal fibroblasts carrying elevated Notch1 activity significantly inhibited melanoma growth and invasion, while those with a null Notch1 promoted melanoma invasion.

CONCLUSION: These findings identify the Notch1 pathway as a molecular determinant that controls the regulatory role of tumor stromal fibroblasts in melanoma skin growth and invasion, unveiling Notch1 signaling as a potential therapeutic target for melanoma and potentially other solid tumors.
NOVEL RNA APTAMERS THAT SPECIFICALLY BIND TO METASTASIS-PRONE PROSTATE CANCER CELL SURFACE TARGETS AND EXERT RAPID CYTOTOXICITY

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BACKGROUND: Prostate cancer is the most common non-skin cancer diagnosed in American men, with about 1 out of every 7 men receiving this diagnosis during his lifetime. For many men, prostate cancer is indolent, while in others, it is aggressive, metastasizing to other tissues of the body before becoming symptomatic. There is a critical need for diagnostic tests that both enable early detection and predict tumor aggressiveness. To address this need, we are utilizing novel technologies to identify, isolate and characterize high affinity nucleic acid oligomers (aptamers) that distinguish between prostate cancers that are likely to remain organ-confined and those with potential to metastasize.

METHODS: We performed subtractive RNA Cell-SELEX using as positive selector a highly metastatic subclone of the prostate cancer cell line LNCapLN3 and as negative selectors both the parent cell line LNCapPro5 and a non-metastasizing subclone, to select for surface ligands specific to the aggressive subclone. The pool of RNA aptamers to be used during the Cell-SELEX were PCR amplified from cDNA library from the general template: TCT CGG ATC CTC AGC GAG TCT G-40(N)-CCG CAT CGT CCT CCC TA, (where N represents 40 random nucleotides) and in vitro transcribed. After 11 SELEX cycles, the pools of RNA aptamers from cycles 0, 4, 9 and 11 were sequenced. High-throughput sequencing data derived from each pool were filtered, clustered, and analyzed. 8 aptamers, representing 4 sequence families, were chosen for further study. Representative relevant and irrelevant aptamers were labeled with Cy3 and used to stain LNCaP-LN3 and LNCaP-Pro5.

RESULTS: Two aptamers (#41 and #63) showed remarkable specificity for binding to the aggressive LNCaP-LN3 cell surface. The same aptamers were specifically cytotoxic toward LNCaP-LN3 cells after a 3-hour incubation, suggesting an antagonist action on a not-yet identified survival pathway. We will present new data on the extent to which these aptamers distinguish between LNCaP-Pro5 (indolent) and LNCaP-LN3 (aggressive) in xenograft tumors in mice in vivo.

CONCLUSION: Aptamer-based technologies have high potential to identify tumor biomarkers in an unbiased way and to assist in diagnosis and treatment of prostate cancer. We have identified RNA aptamers that specifically bind to metastasis-prone prostate cancer cell surface targets, and exert cell-specific toxicity. We propose that these aptamers may help to discriminate between progressive and indolent prostate cancer in clinical applications.
RAD51 SENSITIZES PANCREATIC CANCER CELLS TO AKT INHIBITION


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BACKGROUND: Resistance to therapy in pancreatic ductal adenocarcinoma (PDAC) is often associated with downstream components of KRAS signaling pathways including PI3K/AKT pathway. We sought to determine the effects of inhibition of DNA damage repair recombinase RAD51 on therapeutic sensitivity and resistance to AKT inhibition.

METHODS: RAD51 expression in TMA from human pancreatic tissues determined and analysed for overall survival. Cell lysates from mouse cell lines derived from PanIN and PDA and LMP immunoblotted for RAD51. Orthotopic tumors generated through injection of luciferase tagged Panc1 with RAD51 inhibitor (B02) were analyzed for growth and response using bioluminescent imaging (BLI) in vivo. PDAC cells (i.e., PDA cells with low RAD51 expression and LMP cells with high RAD51 expression; BRCA2 deficient Capan1 and BRCA2 proficient MiaPaca2 cells) were assessed for in vitro sensitivity to AKT inhibitor (MK2206) through apoptosis and proliferation assays. RAD51 knockdown cells treated with MK2206 were also analyzed for cell proliferation and apoptosis.

RESULTS: RAD51 expression confirmed a stepwise increase from normal pancreas to chronic pancreatitis through advancing grade and stage of PDAC. Patients with PDAC tumors expressing high levels of RAD51 had significantly higher tumor grade, stage, and lower OS when compared to those with low RAD51 expression (median survival of 15 months vs 37 months, respectively; P=0.025). BRCA2 deficient Capan1 PDAC cells were sensitive to MK2206 when compared to BRCA2 proficient MiaPaCa2 cells. Bioluminescent imaging (BLI) guided tumor growth analysis confirmed that RAD51 inhibition with B02 treatment decreased tumor growth in PDAC cells. B02 and MK2206 treated PDA and LMP cells showed synergistic downregulation of colony formation in comparison to either B02 or MK2206 drugs treated cells. RAD51 knockdown cells treated with MK2206 showed enhanced cell apoptosis and attenuated cell proliferation.

CONCLUSION: Our findings indicate that RAD51 inhibition increases sensitivity to AKT inhibition. RAD51 expression levels in PDAC tumors may be useful in identification of PDAC patients who will benefit from this therapy.
MTH1: A CRITICAL NON-ONCOGENE ADDICTION IN RAS-DRIVEN CANCER CELLS

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Oncogenic RAS mutations confer multiple malignant traits to cancer cells, many of which are mediated by oncogene-induced reactive oxygen species (ROS). However, oncogenic ROS also create vulnerabilities in the cancer cells, sensitizing them to oxidative DNA damage and strand breaks, which can trigger cellular senescence or cell death. Thus RAS-driven tumor cells require adaptive redox protective mechanisms to inhibit ROS-associated tumor suppression. We previously reported that MutT Homolog 1 (MTH1), the mammalian 8-oxodGTPase, comprises one such critical adaptation. We have shown MTH1 is important for facilitating the full gamut of RAS-driven malignancy by promoting evasion of the first barrier to transformation, viz. oncogene-induced senescence (OIS), enhancing RAS-mediated transformation and related pro-malignant traits, and maintaining proliferation and tumorigenicity in established RAS-driven tumor cells. Recently chemical inhibitors against MTH1 have been developed, although there is some controversy surrounding their efficacy and mode of action. Our work here discusses RAS regulation of MTH1 expression, and the molecular contexts under which MTH1 inhibition can synergize with oncogenic oxidative stress in RAS-driven tumor cells for optimal tumor suppressive response.
BET BROMODOMAIN PROTEIN INHIBITION IS A NOVEL MOLECULAR THERAPEUTIC STRATEGY FOR ESOPHAGEAL ADENOCARCINOMA

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BACKGROUND: The incidence of esophageal adenocarcinoma (EAC) has been on the rise in the United States and other western countries over the past 30 years. Given the poor prognosis for EAC, it is imperative to develop effective treatment strategies and improve clinical management of EAC. BET proteins are epigenetic regulators for Hedgehog pathway and Hedgehog target MYC. Targeting MYC expression through BET inhibition resulted in anti-tumoral effects in various cancers, partly through regulating Hedgehog pathway transcriptional output.

METHODS: In this study, the effects of suppressing BET proteins are achieved by BET inhibitor i-BET151, or siRNA knocking down of BRD2, BRD3, and BRD4. The proliferation, apoptosis, viability, colony formation and migration ability were assessed in four EAC cell lines and two EAC primary cells. The molecular changes were quantified by quantitative RT-PCR, western blot analysis, immunofluorescence and immunohistochemistry. Furthermore, the efficacy of i-BET151 against EAC preclinical models was evaluated in vivo.

RESULTS: Our studies indicate that i-BET151 or BRD2/BRD4 knockdown decreased proliferation and self-renewal capacity of EAC cells. Treatment of EAC cell lines with i-BET151 significantly reduced cell proliferation and preferentially induced apoptosis in cells. Declined expression levels of developmental pathways, such as Hedgehog/Gli1 and WNT/Beta-Catenin, were observed in EAC cells after i-BET151 treatment or BET bromodomain proteins knockdown compared to the corresponding controls. The transcriptional output of Hedgehog/Gli1 is an epigenetic target of BET bromodomain proteins in EAC cells, but not for WNT/Beta-Catenin signaling pathway. i-BET151 treatment of EAC cell lines down-regulates Gli1 expression and results in a transcriptional deregulation of Gli1 targets, and also significantly altered expression of the genes involved in cancer stemness. Significantly, we investigated that i-BET151 abrogates the growth of three independent EAC PDX models in vivo.

CONCLUSION: Our preclinical data provide evidence to pursue testing BET inhibitors, such as i-BET151, as a novel molecular therapeutic strategy for patients with EAC overexpressing Hedgehog/Gli1.
DEREGULATION OF STING SIGNALING IN COLORECTAL CARCINOMA CONSTRAINS DNA-DAMAGE RESPONSES AND CORRELATES WITH TUMORIGENESIS

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BACKGROUND: STING (stimulator of interferon genes) has been shown to be critical for controlling anti-viral responses, as well as anti-tumor adaptive immunity but little is known regarding its regulation in human tumors.

METHODS: Human colorectal carcinoma derived cells were analyzed for STING signaling as well as their susceptibility to oncolytic viral infection.

RESULTS: STING-signaling is recurrently suppressed in a wide variety of cancers, including colorectal carcinoma. Loss of STING signaling impeded DNA damage responses accountable for generating key cytokines that facilitate tissue repair and anti-tumor T cell priming, such as type I interferon (IFN). Correspondingly, defective STING function was also highly predictive of effectual DNA virus-mediated oncolytic activity.

CONCLUSION: Impaired STING responses may enable damaged cells to evade host immnosurveillance processes, although provides a critical prognostic measurement that could help predict the outcome to effective oncoviral therapy.
THE PIVOTAL ROLE OF TAFII250 IN AML1-ETO EXPRESSING LEUKEMIA DEVELOPMENT

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BACKGROUND: Rearrangement between chromosomes 8 and 21 is the most commonly observed chromosomal translocation. In AML patients, it leads to the formation of a novel fusion transcription factor AML1-ETO. AML1-ETO has no enzymatic function, thus targeting AML1-ETO directly is technically difficult. Our lab has reported that the acetylation of AML1-ETO contributes to leukemogenesis and acetylated AML1-ETO selectively binds to TAFII250 which is part of basal transcription machinery.

METHODS: Here, we used Kasumi-1 and SKNO-1 cell lines derived from AML patients with AML1-ETO expressing and AE9a cell line developed from bone marrow cells of mice injected with bone marrow cells infected with AE9a to perform in vitro and in vivo study.

RESULTS: We found that TAFII250 is physically associated with AML1-ETO in leukemia cells and the association plays pivotal roles in the proliferation and apoptosis of these cells. Further, TAFII250 promotes the interaction of AML1-ETO with CBFB (core binding factor beta subunit) which stabilizes the binding of AML1-ETO to DNA. Loss of TAFII250 impairs the interaction of CBFB with AML1-ETO and blocks the recruitment of AML1-ETO to its target genes, interfering with the expression of target genes. Most importantly, the depletion of TAFII250 has negative effect on the self-renewal of stem cells, promotes myeloid differentiation and impairs leukemia development.

CONCLUSION: Together, these results reveal an essential role of TAFII250 in leukemogenesis and imply that TAFII250 might act as a novel therapeutic target for AML1-ETO expressing AML.
BIOLUMINESCENCE/FLUORESCENCE DUAL-MODAL ASSAY FOR RAPID DETECTION AND FURTHER CHARACTERIZATION OF CIRCULATING TUMOR CELLS

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BACKGROUND: The enumeration of circulating tumor cells (CTCs) in metastatic cancer patients provides potential values in prediction of cancer progression and monitoring therapeutic efficacy. Additionally, the molecular characterization of CTCs enables investigation of patient specific cancer-omics profiles for improved diagnosis and personalized treatment. Here we report a novel dual-modal assay which enables rapid detection of CTCs followed by either single-cell analysis or biobank of these cells.

METHODS: Antibody mimetics (targeting moiety) are genetically fused with bioluminescence proteins, and later chemically conjugated with fluorescent dye to form dual-imaging sensors. Specificity, sensitivity, and cytotoxicity of dual-imaging sensors are evaluated.

RESULTS: We demonstrate that our dual-modal assay are able to specifically target CTCs with high sensitivity, and using multi-marker combination strategy effectively increases sensitivity in CTC detection. In tumor cell spiking experiment, our approach has successfully identified spiked cells in the human whole blood, and subsequently these spiked cells are able to be expanded in culture or accurately picked up for single-cell analysis.

CONCLUSION: Our technique may provide a promising tool in detection and characterization of CTCs for cancer management.
INTEGRATOR’S ROLES IN THE 3’END PROCESSING OF MRNA

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BACKGROUND: Integrator complex is emerging as a key factor in the epigenetic regulation of gene transcription in multi-cellular organisms, and mutations in Integrator subunits have been discovered in a variety of cancers. However, only until recently, the tip of the iceberg of Integrator’s potential functions in epigenetic gene regulation has been revealed: Integrator plays a critical role in transcription initiation and pause release following activation; Integrator could also indirectly affect transcription activation and mRNA splicing by modulating 3’ end processing of non-coding RNAs, such as eRNAs and usnRNAs, respectively. In this study, we are investigating another possible mechanism which involves transcription termination and mRNA polyadenylation.

METHODS: We compared the differences in mRNA termination and polyadenylation in wildtype Hela cells and Integrator subunit (Ints11) knockdown cells by high-throughput polyA RNA sequencing (RNA-seq) and 3' region extraction and deep sequencing (3'READS). We also validated several candidate genes in polyA signal (PAS) reporter assays. In order to discriminate potential mechanisms of direct mRNA-cutting by Ints11 nuclease activity from indirect effects on termination and polyadenylation factor recruitment, we investigated whether the phenotype could be rescued by overexpressing the enzymatic-dead version of Ints11 (E203Q mutant). We also look at Integrator glabla localization, both on the chromatin and on the RNA by chromatin immunoprecipitation sequencing (ChIP-seq) and RNA immunoprecipitation (RIP-seq) to understand Integrator’s function at the 3’ end of mRNAs. In addition, we analyzed whether the extended form of mRNAs have an impact on translation by polysome assay.

RESULTS: Besides 686 differentially expressed protein-coding genes (fold change > 2) in Ints11 knockdown Hela cells comparing with WT cells, we detected 30 additional mRNA with extended 3’ end. 17 of them can be rescued by the overexpression of E203Q mutant; while 13 of them cannot be fully rescued by E203Q mutant overexpression but the extension can be reverted by WT Ints11 overexpression. In polyA signal reporter assays, we picked four genes to validate that the canonical PAS sequence (AAUAAA) is required for Int11-dependent proximal PAS preference. We did not observe significant Int11 localization at the 3’ end of these genes on the chromatin, but Int11 is bound to the 3’ end of the RNA. Polysome assay detected the extended forms of RNA in the actively translated fractions.

CONCLUSION: Integrator is involved in the 3’ end processing of a group of mRNAs both directly and indirectly. The absence of Ints11 leads to the usage of distal PAS site in these genes to give mRNA with an extended 3’ end that can be translated. The direct effect is probably exerted through the nuclease enzymatic activity of Ints11 subunit. The indirect effect could partially due to the alternation of the expression level of several RNA 3’ end binding proteins. Since the extended 3’ end of mRNA usually contains rich regulatory information, and several cancers and diseases are known to prefer proximal PAS sites usage, Integrator might be exploited to modulate mRNA length in cancer cells.
COOPERATIVE EFFECTS OF HAPLOINSUFFICIENT ASXL1 AND NF1 IN ACUTE MYELOID LEUKEMIA TRANSFORMATION

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BACKGROUND: Concomitant mutations in genes involved in epigenetic regulation (ASXL1, SUZ12, DNMT3A, IDH2, TET2) and signaling pathways (CBL, JAK2, MPL, NF1) have been reported clinically in patients with myeloid malignancies. ASXL1 gene is mutated/deleted with high frequencies in all spectrum of myeloid malignancies, and its alterations are associated with poor prognosis. Deletions/mutations of NF1 gene, a negative regulator of RAS-GTP, were found in 5% of myeloid malignancies. NF1 mutations lead to hyperactivation of RAS pathway. The objective of this project is to determine the cooperative effects of compound haploinsufficiency of NF1 and ASXL1 on AML initiation/progression using novel murine models.

METHODS: A serial hematopoietic analyses were performed, including peripheral blood counts, blood smear, morphology, flow cytometry and histology. In vivo tumor transfer assays were used to evaluate the malignant nature of the infiltrated cells in moribund/diseased Asxl1+/−;Nf1+/− mice. To determine the molecular mechanisms by which haploinsufficient Asxl1 and Nf1 cooperate in promoting AML transformation, we performed western blotting and RNA-seq to examine the dysregulated histone modifications and to survey the differentially expressed genes in each of the genotypes of hematopoietic stem/progenitor (HSPC, Lin-c-Kit+, LK) cells.

RESULTS: Asxl1+/−;Nf1+/− mice had a worse survival rate compared to all other three groups of control mice (WT, Nf1+/−, and Asxl1+/−). Compound haploinsufficiency of Asxl1 and Nf1 results in progressive and lethal AML as reflected by >20% of blasts in their bone marrow. Asxl1+/−;Nf1+/− mice also exhibited an elevated white blood cell counts with anemia and thrombocytopenia, as well as spleno-hepatomegaly. Infiltration of immatured myeloid cells was prominent in the spleens and the livers of Asxl1+/−;Nf1+/− mice. Tumor transfer assay demonstrated that these leukemic cells were transferable to the sub-lethal irradiated wild-type 1st and 2nd recipient mice. RNA-seq analysis showed an unique signature of Asxl1+/−;Nf1+/− LK cells compared to other genotypes of LK cells. Gene set enrichment analysis showed upregulation of negative regulators for HSPC and myeloid differentiation. Furthermore, biochemistry studies revealed a dramatic reduction of the global levels of trimethylation of histone H3 lysine 27 (H3K27me3) in Asxl1+/−;Nf1+/− LK cells. Interestingly, the expression of EED, a PRC2 component, was significantly lower in Asxl1+/−;Nf1+/− LK cells than that in other genotypes of LK cells. Further studies are on the way to determine if the reduced level of EED results in further reduction in PRC2 recruitment to the chromatin and diminishing H3K27me3 marks in vivo.

CONCLUSION: Our studies provide compelling evidence that compound haploinsufficiency of Asxl1 and Nf1 leads to AML initiation/progression by altering the expression of genes critical for leukemogenesis due to diminished H3K27me3 deposition. This preclinical model system provides us an ideal platform for testing of novel therapeutics for AML.
EFFECTS OF SINGLE, DOUBLE AND TRIBLE COMBINATIONS OF IMATINIB, ABT-737 AND CHLOROQUINE ON GASTROINTESTINAL STROMAL TUMOR T1 CELLS

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BACKGROUND: GIST is the most common mesenchymal neoplasm in gastrointestinal tract. KIT mutations are found in 85% of GIST and platelet-derived growth factor receptor A (PDGFRA) mutations are found in 7% of GIST. Although Imatinib is quite effective in extending median overall survival (OS) to 57 months, it is generally not curative. 10-20% of patients exhibit primary resistance and immediate progression and 50% of Imatinib-sensitive patients develop resistance and progression in 2 years. New therapeutical strategies focusing on improving the effects of Imatinib are needed. Current trends in the treatment of GIST are based on drug combinations which result in improved responses and less adverse effects. A synergistic effect can be reached through a combination of drugs with different antitumor mechanism, such as apoptosis and autophagy. Here, we are seeking to determine the synergistic or antagonistic effects of Imatinib, ABT-737 and chloroquine in GIST-T1 cells line.

METHODS: GIST-T1 cells were treated with Imatinib, ABT-737 and Chloroquine as single agent and different combinations to assess their effects on cell viability. First, the IC50 for each agent and IC50 ratio between the three drugs were determined. Two doses above the IC50 and three doses below the IC50 of each drug were chosen to treat the cells. The adjacent concentrations of each drug had 2 or 3 times of difference. According to the results from Chloroquine and ABT-737, three concentrations were chosen to combine with imatinib. The cell viability of GIST-T1 cells in single or different combinations of Imatinib, ABT-737 and Chloroquine was measured by MTS. Synergism was analyzed by isobologram software in combinational groups. The apoptosis (PARP, Caspase-3) and autophagy (LC3-II, beclin 1) were measured by western blot. Cell cycle analysis was performed by flow cytometry.

RESULTS: The IC50 of Imatinib, ABT-737 and Chloroquine was 0.05µM, 10µM, 43µM, respectively. Single agent treatment reduced the cell viability of GIST-T1 cells in a time- and dose-dependent manner. Double combination of drugs synergistically decreases cell viability in a time- and dose-dependent manner. Isobologram analysis revealed strongly synergistic drug interaction, with combination indices <0.5 for most of double and triple combinations. Thus, chloroquine and ABT-737 with clinically relevant concentration in vitro have antitumor activity and are synergistic with imatinib.

CONCLUSION: The potent activity, together with the exclusive mechanistic profile, provides the rationale for the clinical evaluation of these drug combinations in gastrointestinal stromal tumor.
CLINICAL RESEARCH
SLEEP QUALITY MEDIATES THE RELATIONSHIP BETWEEN CANCER-RELATED INTRUSIVE THOUGHTS AND FATIGUE SEVERITY IN NON-METASTATIC BREAST CANCER PATIENTS

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BACKGROUND: Women recently diagnosed with breast cancer (BCa) report cancer-related intrusive thoughts, fatigue, and poor sleep quality prior to the start of adjuvant therapy. The interrelationships among these variables have been less studied. This study tests the hypothesis that intrusive thoughts relate to greater fatigue through their influence on sleep quality in women with non-metastatic BCa in the weeks after surgery and before beginning adjuvant therapy.

METHOD: Women (N=147) with non-metastatic stage 0-III BCa were recruited 2-10 weeks post-surgery to participate in a psychosocial intervention prior to adjuvant therapy. Women completed the Impact of Events Scale (intrusion scale), a shortened 5-item inventory of the Pittsburgh Sleep Quality Index and the Fatigue Symptom Inventory (severity scale). Bootstrapping analyses (using 1000 bootstrapped samples) tested the model of sleep quality as the mediator of the relationship between intrusive thoughts and fatigue severity.

RESULT: There was a significant indirect effect of cancer-related intrusive thoughts on fatigue severity through sleep quality when controlling for age, time since surgery, disease stage, type of surgery, education and income, b=3.3491, 95% CI [2.2421, 4.6055], with a large effect size, $\kappa^2=.3458$, 95% CI [.2366, .4758].

CONCLUSION: In the weeks after surgery, sleep quality may explain the relationship between cancer-specific intrusive thoughts and fatigue severity above and beyond the physical effects of surgery, disease stage, and age in non-metastatic BCa patients. Future interventions targeting intrusive thoughts early in treatment may improve sleep quality, which in turn may improve fatigue levels.
SURGERY FOR METASTATIC ESOPHAGEAL CANCER: IS LONG-TERM SURVIVAL FEASIBLE?

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BACKGROUND: Patients presenting with metastatic esophageal cancer have poor prognosis and are generally managed with palliative chemoradiotherapy. The role of surgical resection in selected patients with favorable response to definitive chemotherapy has not been defined.

METHOD: We performed a retrospective review of a prospectively-collected database of patients undergoing esophagectomy at a single academic institution between 1999-2012. We identified patients who underwent esophagectomy after initially presenting with metastatic esophageal cancer and undergoing chemotherapy with radiographic evidence of a favorable clinical response.

RESULT: Five patients were identified who initially presented with stage IV esophageal cancer, underwent chemotherapy with a positive clinical response, and subsequently underwent esophagectomy. Of this group, 4 patients (80%) had adenocarcinoma and 1 (20%) had squamous cell carcinoma of the esophagus. The most common site of primary tumor was in the gastroesophageal junction (n=3, 60%), followed by middle (n=1, 20%) and distal esophagus (n=1, 20%). All patients initially presented with solitary metastases. Sites of metastases included the liver (n=3, 60%), stomach (n=1, 20%), and bone (n=1, 20%). Metastases were detected by biopsy in 60% (n=3) and radiographically in 40% (n=2) of cases. All patients underwent transhiatal esophagectomy with a median time from diagnosis to surgery of 11 months (range 2-14 months). Complete (R0) resection was achieved in all cases. Final pathology demonstrated stage III in 2 cases (40%), stage II in 2 cases (40%), and 1 patient (20%) had a complete response to chemotherapy (Stage 0). There were no 30-day perioperative deaths and median length of stay was 9 days (range 7-26). Median survival after esophagectomy was 37 months (range, 14-62 months), with 1-year, 3-year, and 5-year overall survival of 100% (n=5), 40% (n=2), and 20% (n=1), respectively. Notably, median survival from time of diagnosis was 48 months (range 24-73).

CONCLUSION: In a select group of patients with metastatic esophageal cancer with favorable response to initial chemotherapy, esophagectomy with complete (R0) resection may result in long-term survival. The impact of surgery in these cases of metastatic esophageal cancer should be further explored.
PANCREATIC NEUROENDOCRINE TUMORS (PANNETS): SURVIVAL ANALYSIS COMPARING SURGICAL RESECTION VS. NON-SURGICAL MANAGEMENT

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BACKGROUND: The optimal management of PNETs remains controversial. This study aims to compare survival of patients with PNETs undergoing either surgical resection or non-surgical management.

METHOD: A comprehensive search of MEDLINE, EMBASE, PubMed, SCOPUS and the Cochrane database was conducted (2006-present). All studies for patients with panNETs comparing surgical with non-surgical management were included. The STROBE checklist was used for quality assessment of included studies. Pooled risk ratios (RR) along with 95% confidence intervals (CI) for overall survival (OS) at 1, 3, and 5 years were calculated.

RESULT: Our search strategy yielded 917 studies, out of which 11 studies met our inclusion criteria. Overall, 10 studies with 3,098 panNET patients were included; 1,491 underwent resection and 1,607 underwent non-surgical management. Meta-analysis showed statistically significant improved OS in patients undergoing resection compared with non-surgical management at 1 (RR=1.281, CI: 1.064–1.542, p = 0.009), 3 (RR=1.837, CI: 1.594–2.117, p < 0.001), and 5 years (RR=2.103, CI: 1.50 – 2.945, p < 0.001). Subgroup analysis of patients with nonfunctioning panNETs also showed significantly improved OS in the resection group at 1 (RR=1.240, CI: 0.778 – 1.975 p = 0.366), 3 (RR=1.847, CI: 1.477–2.309, p < 0.001), and 5 years (RR=1.767, CI: 1.068 – 2.924, p = 0.027). Subgroup analysis of patients with panNETs ≤ 2 cm in size, all of which were nonfunctioning, also showed improved survival in the resection group at 1 (RR=1.177, CI: 0.441 – 3.147 p = 0.745), 3 (RR=1.695 CI: 1.269 – 2.264, p < 0.001), and 5 years (RR=2.210 CI: 1.749 – 2.791 p < 0.001). In patients with tumors <2 cm, although lymph node status and histological grade were heterogeneous, resection of the primary tumor was still associated with improved OS.

CONCLUSION: Surgical resection of panNETs is associated with improved OS compared with non-surgical management. The improved OS with surgical resection is seen in patients with non-functional tumors, tumors greater than or less than 2 cm. Prospective, randomized clinical trials are needed to further detail and support these results.
A CROSS-SECTIONAL ANALYSIS OF COPING WITH SIGNIFICANT PAIN SEVERITY AND INTERFERENCE IN NON-METASTATIC BREAST CANCER PATIENTS

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BACKGROUND: Women with breast cancer (BCa) often struggle with clinically significant levels of pain severity and interference. Little is known about the relationship between coping and pain across BCa diagnosis, treatment, and recovery. We explored associations between coping and clinically significant pain severity (CSPS) and interference (CSPI) during the first year of the BCa experience post-diagnosis.

METHOD: Stage 0-III BCa patients were recruited 2-12 weeks post-surgery. At study entry (T1), 6 (T2), and 12 (T3) months follow-up, women completed the Brief COPE measure of coping responses to BCa diagnosis and treatment, and the Brief Pain Inventory (BPI). Cross-sectional linear regressions on Brief COPE and BPI scores were run on a subset of women with CSPS and CSPI (BPI severity and interference scores ≥3/10) controlling for age, ethnicity, BCa stage, pain medication, days since surgery, and treatment received (i.e., chemotherapy or radiation in the last 3 weeks).

RESULT: At T1, women had moderate levels of CSPS (N=72, M=4.25, SD=1.43) and CSPI (N=67, M=5.08, SD=1.59). Report of denial was associated with higher levels of CSPS within this subset of clinically elevated cases (β=0.44, t(72)=4.06, p<.01). At T2, women had similar levels of CSPS (N=37, M=4.49, SD=1.80) and CSPI (N=33, M=5.37, SD=2.04). Denial remained associated with greater levels of CSPS (β=0.42, t(37)=2.36, p<.05), while venting was associated with higher levels of both CSPS (β=0.43, t(37)=2.14, p<.05) and CSPI (β=0.44, t(33)=2.47, p<.05) in these clinically elevated cases. At T3, levels of CSPS (N=34, M=4.65, SD=1.61) and CSPI (N=26, M=5.00, SD=1.57) were largely unchanged. Planning was associated with higher levels of CSPS (β=0.48, t(34)=2.59, p<.05), while denial was associated with higher levels of CSPI (β=0.50, t(26)=2.63, p<.05) in this subset of clinically elevated cases.

CONCLUSION: Certain coping methods are associated with pain reports among women with CSPS and CSPI throughout the BCa experience post-diagnosis. Use of denial was consistently associated with greater pain reports during the first year of treatment for primary BCa (T1, T2, and T3), while venting and planning related to pain as women were completing adjuvant therapy (T2 and T3). Future psychosocial interventions for non-metastatic BCa patients should promote acceptance-based practices to curb maladaptive coping among women reporting CSPS and CSPI.
THE PARIS SYSTEM: RECLASSIFICATION OF NON-NEGATIVE URINE CYTOLOGY

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BACKGROUND: Urine cytology is a simple, inexpensive tool and a key element in the surveillance of patients with urothelial carcinoma (UC). The American Urological Association guidelines recommends the use of urinary cytology to screen and evaluate patients at high risk for UC and monitor recurrence, progression, or treatment response. In 2013, the International Academy of Cytology (IAC) and The American Society of Cytopathology (ASC) presented the Paris System (PS) for reporting urine cytology at the International Cytology Congress. The system categories have been recently defined and include: Adequacy, Negative for High-Grade Urothelial Carcinoma (NHGUC), Atypical Urothelial Cells (AUC), Suspicious for High-Grade UC (SHGUC), High Grade UC (HGUC), Low-Grade Urothelial Neoplasm (LGUN), Other malignancies.

METHOD: We retrospectively reviewed non-negative urine cytology cases with concomitant biopsies diagnosed between January 2013 and August 2015 at the University of Miami Hospital (UMH). The diagnoses were re-classified using the PS.

RESULT: Of the 1846 urine cytology cases diagnosed during the study period, 1441 were negative (78%) and 405 (22%) were originally interpreted as atypical, suspicious or malignant. The study cohort consist of 110 cases which had available concomitant biopsy results. NHGUC represented 4% (4/110), AUC 33% (37/110), SHGUC 28% (31/110), HGUC 31% (34/110) and LGUN 4% (4/110). High-grade malignancy rates for AUC, SHGUC and HGUC are 60%, 97% and 85%, respectively. Only one LGUN case showed low-grade UC, the remaining were high-grade UC (Table 1).

<table>
<thead>
<tr>
<th>Paris Category</th>
<th>% (# cases)</th>
<th>High Grade Malignancy Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHGUC</td>
<td>4(4)</td>
<td>0</td>
</tr>
<tr>
<td>AUC</td>
<td>33(37)</td>
<td>60</td>
</tr>
<tr>
<td>SHGUC</td>
<td>28(31)</td>
<td>97</td>
</tr>
<tr>
<td>HGUC</td>
<td>31(34)</td>
<td>85</td>
</tr>
<tr>
<td>LGUN</td>
<td>4(4)</td>
<td>75</td>
</tr>
<tr>
<td>Total</td>
<td>100 (110)</td>
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</tbody>
</table>

CONCLUSION: The adoption of the Paris System offers standardization for urine cytology reporting. All AUC and SHGUC cases that were probed to be malignant on biopsy, demonstrated high grade UC. LGUN may be controversial due to the challenge of diagnosing low grade UC in urine cytology. Our experience performing this study allowed us to start the learning curve to apply the Paris System. The cytopathologists will need to adapt to the new criteria and terminology.
SOCIAL WELL-BEING IS ASSOCIATED WITH PRO-INFLAMMATORY AND PRO-METASTATIC LEUKOCYTE GENE EXPRESSION AFTER SURGERY FOR BREAST CANCER

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**BACKGROUND:** Perceiving adequate social support is associated with better physical health and longer survival after breast cancer diagnosis. However, biobehavioral mechanisms linking social experience to the health of breast cancer patients are poorly understood. Existing literature indicates that social adversity relates to heightened pro-inflammatory leukocyte gene expression, which has also been associated with cancer disease progression. However, no studies have tested whether social well-being relates to less pro-inflammatory gene expression after surgery for breast cancer, which could imply processes fostering salutary health effects that begin early in treatment.

**METHOD:** Women (N = 78) were assessed 2-12 weeks after surgery for breast cancer with the Social/Family Well-Being subscale of the Functional Assessment of Cancer Therapy – Breast (FACT-B). Leukocyte gene expression was measured by microarray analysis of peripheral blood mononuclear cells. Multiple regression analyses controlling for age, stage, education, time since surgery, and body mass index (BMI) tested whether social well-being was associated with leukocyte expression of pro-inflammatory (cytokines, chemokines) and pro-metastatic (tissue remodeling metalloproteases) genes.

**RESULT:** Multiple regression analyses showed that greater social well-being was associated with less pro-inflammatory cytokine/chemokine (IL-1A, CCL20) and pro-metastatic (MMP-9, LMNA) gene expression, including expression for the COX-2 pathway (PTGS2) (all ps<0.05).

**CONCLUSION:** Results add to prior findings that social experience relates to leukocyte gene expression and document these associations in the period after surgery for breast cancer, suggesting a mechanism through which social experiences early in primary treatment relate to health status. Importantly, this study demonstrates that effects of social well-being on gene expression hold after controlling for several correlates of inflammation, including age, disease stage, and BMI. Future research should test directionality of this relationship and whether social well-being and gene expression changes during treatment predict longer-term health outcomes. Studies should also be designed to test whether interventions to strengthen social relationships and well-being lower inflammation early in breast cancer treatment, when important processes may be unfolding.
PERFORMANCE OF THE AFIRMA GENE EXPRESSION CLASSIFIER IN THE EVALUATION OF CYTOLOGICALLY INDETERMINATE THYROID NODULES: AN INSTITUTIONAL APPROACH


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BACKGROUND: Molecular testing of thyroid fine-needle aspiration (FNA) specimens has the potential to improve diagnostic yield for the 15-30% of cases with indeterminate cytology. The Afirma Gene Expression Classifier (GEC) reports a negative predictive value (NPV) of 94-95% and positive predictive value (PPV) 37-38% for indeterminate nodules, identifying aspirates with the greatest risk of malignancy while sparing most patients from unnecessary surgery. This study reviews the authors’ institutional experience with Afirma in an academic medical center.

METHOD: A cohort of 939 thyroid FNAs performed from 2013 to 2015 was selected from the study files and relevant information was recorded and analyzed. 240 of these aspirates were diagnosed as atypia of undetermined significance/follicular lesion of undetermined significance (Bethesda category III). Of these, 69 indeterminate aspirates had material collected for GEC analysis. Follow-up was either clinical or surgical.

RESULT: Of the 69 specimens, 2 (2.9%) contained insufficient mRNA, leaving 67 Afirma results for analysis. Of these, 24 (35.8%) were benign and 43 (64.2%) were suspicious. 19 patients diagnosed with GEC-suspicious nodules underwent surgery; malignancy was confirmed in 8 (42.1%) of these cases and 11 (57.9%) cases were benign. All GEC-benign nodules (n=24) and only those GEC-suspicious nodules that underwent surgery (n=19) were included for analysis. Based on clinical follow-up of benign cases for a median of 5.8 months with no false-negative results: sensitivity=100%; specificity= 68.6%; prevalence of malignancy=18.6%; NPV of benign GEC= 100%; PPV of suspicious GEC= 42.1%, accuracy=74.4%.

CONCLUSION: In this study, the Afirma GEC demonstrates a lower than expected malignancy rate within GEC-suspicious nodules (institutional prevalence of malignancy for Bethesda category III FNAs=37%). While Afirma is useful to rule out malignancy, a high rate of unnecessary surgery was evident. For GEC-suspicious nodules, further confirmatory tests should be performed prior to definitive surgery.
MICRORNAS AND CIRCULATING FACTORS LINKED TO CANCER ASSOCIATED FIBROBLASTS MAY BE CRITICAL TO BREAST CANCER PROGRESSION AND METASTASIS


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BACKGROUND: Tumor metastasis is the main cause of breast cancer mortality. Increasing evidence demonstrates stromal cells play pivotal roles to promote breast cancer progression and metastasis. Breast cancer stroma is comprised mainly of Cancer Associated Fibroblasts (CAFs). CAFs secrete various growth factors and cytokines that promote breast cancer progression and metastasis. It also activates ERK 1/2 MAPK signaling in cancer cells. Hyperactivation of MAPK facilitates loss of ER, epithelial to mesenchymal transition (EMT) – an essential step in the metastatic process, and breast cancer progression. Recently, we identified a patient-derived hMAPK-microRNA signature that contains microRNAs known to regulate breast cancer associated genes. This signature identifies the vast majority of ER- breast cancers and a subset of more aggressive ER+ breast cancer that associates with poor breast cancer outcome, reduced recurrence-free survival and disease-specific survival. All tumors with this signature have significantly higher stromal and immune infiltrate scores.

METHODS/RESULTS: We have established primary breast CAF lines, from Luminal A breast cancers (indolent), and from ER-/Her2 amplified and from triple negative cancers (aggressive). The CAFs differentially express several hMAPK-microRNAs compared to dissociated tumor cells. Importantly secreted hMAPK-microRNAs from “aggressive” CAFs are taken up by breast cancer cells whereupon they repress their targets and alter phenotype while normal human mammary fibroblasts (HMFs) and CAFs from luminal A tumors (“indolent” CAFs) do not secrete these microRNAs. Collectively these data suggest that different CAF populations have distinct abilities to influence the phenotype and behavior of associated cancer cells.

Recently, we identified a novel class of circulating cells in the blood of most breast cancer patients with metastases –CAFs (cCAFs). Patients with cured disease did not have these cCAFs, while some patients with breast cancer but no overt metastasis did. In addition, we have found that the patients with metastasis and higher incidence of cCAFs in their blood have an over-expression of SDF-1. We have also shown that CAFs from aggressive breast tumors secrete higher levels of SDF-1. It is already known that CAF secreted SDF-1 plays a critical role in tumor metastasis. We measured the SDF-1 levels from patients’ blood at different stages of breast cancer patients and again observed that patients with higher incidence of circulating CAFs had a higher expression of SDF-1. Finally, we examined the expression of other tumor-promoting soluble factors and miRNAs secreted by CAFs in the patient serum samples.

CONCLUSION: Our results establish a clear link between SDF-1, circulating CAFs, and CAF-secreted factors with breast cancer metastasis. We suggest that cCAFs may represent “aggressive” CAFs that facilitate breast cancer metastasis, at least in part, via CAF-secreted factors.
DRIVER MUTATIONS IN UVEAL MELANOMA: ASSOCIATIONS WITH GENE EXPRESSION PROFILE AND PATIENT OUTCOMES

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BACKGROUND: Frequent mutations have been described in the following 5 genes in uveal melanoma (UM): BAP1, EIF1AX, GNA11, GNAQ and SF3B1. Understanding the prognostic significance of these mutations could facilitate their use in precision medicine.

METHODS: Retrospective study of UM patients treated by enucleation by a single ocular oncologist between November 1, 1998 and July 31, 2014. Clinicopathologic features, patient outcomes, GEP classification (class 1 or class 2) and mutation status were recorded.

RESULTS: The study cohort comprised 81 participants. Their mean age was 61.5 years, and 37% (30 of 81) were female. The GEP classification was class 1 in 35 (43%), class 2 in 42 (52%) and unknown in 4 (5%) cases. BAP1 mutations were identified in 29 of 64 (45%), GNAQ mutations in 36 of 81 (44%), GNA11 mutations in 36 of 81 (44%), SF3B1 mutations in 19 of 81 (24%) and EIF1AX mutations in 14 of 81 (17%) cases. Sixteen of the mutations in BAP1 and 6 of the mutations in EIF1AX were previously unreported in UM. GNAQ and GNA11 mutations were mutually exclusive. BAP1, SF3B1 and EIF1AX mutations were almost mutually exclusive with each other. Using multiple regression analysis, BAP1 mutations were associated with Class 2 GEP (P<0.001) and older patient age (P=0.007). EIF1AX mutations were associated with Class 1 GEP and absence of ciliary body involvement (P=0.03 for both). SF3B1 mutations were associated with younger patient age (P=0.006). GNAQ mutations were associated with absence of ciliary body involvement (P=0.008) and greater largest basal diameter (P=0.04). GNA11 mutations were not associated with any of the analyzed features. Using Cox proportional hazards modeling, class 2 GEP was the prognostic factor most strongly associated with metastasis (relative risk, 9.4; 95% CI, 3.1-28.5) and melanoma-specific mortality (relative risk, 15.7; 95% CI, 3.6-69.1) (P<0.001 for both). After excluding GEP class, the presence of BAP1 mutations was the factor most strongly associated with metastasis (relative risk, 10.6; 95% CI, 3.4-33.5) and melanoma-specific mortality (relative risk, 9.0; 95% CI, 2.8-29.2) (P<0.001 for both).

CONCLUSION: BAP1, SF3B1 and EIF1AX mutations occur during UM tumor progression in an almost mutually exclusive manner and are associated with different levels of metastatic risk. These mutations may have value as prognostic markers in UM.
SLEEVE GASTRECTOMY: UNANTICIPATED FINDINGS IN THE PATHOLOGY REVIEW. MORE THAN ANYONE EXPECTS!

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University of Miami Miller School of Medicine/Jackson Memorial Hospital.

BACKGROUND: Sleeve gastrectomy is a surgical weight-loss procedure which is rapidly becoming the most common treatment option for bariatric patients with a BMI of 60 or higher. This procedure is usually performed laparoscopically and involves the removal of about 75-80% of the stomach along the greater curvature creating a narrow gastric tube or “sleeve”. The University of Miami Hospital (UMH) is the only university-based bariatric center in the region and one of the most sought after destination for bariatric surgery. The patients that undergo these surgeries are evaluated extensively and presumed not to have any significant gastric pathology. The aim of this study is to review the pathologic findings seen in sleeve gastrectomy cases over a 2 year period.

METHODS: A retrospective review of the pathology database at University of Miami Hospital (UMH) from August 2013-August 2015 was performed for all sleeve gastrectomy cases including the pathologic diagnosis, gross description and demographic information.

RESULTS: There was a total of 524 specimens identified in the two year period. The patients ranged from 16 to 79 years (mean age of 44 years). Female patients were more likely to have this procedure (378) than males (146). The most prevalent diagnosis was chronic gastritis; 40.6% (213/524) and follow by active chronic gastritis; 7.5% (40/524). Additional findings included Helicobacter pylori infection, 3.2% (17/524) gastric fundic gland polyps; 2.8% (15/524), intestinal metaplasia without dysplasia in 2.26% (10/524) and autoimmune atrophic gastritis; 0.3% (2/524). Congestion is seen in 42.7% of cases (224/524), which is mostly procedure related. Neoplastic tumors were identified in 1.7%, 8 gastrointestinal stromal tumor (GIST), and 1 leiomyoma. No malignancy were identified. Non-specific histopathologic changes were found in 12% of the specimen (66/524).

CONCLUSION: The demographic population that is seen at UMH is diverse and there are a variety of additional or incidental findings which usually requires follow up. The most frequent diagnosis is chronic gastritis and congestion. The neoplastic unexpected findings include 8 gastrointestinal stromal tumors and 1 leiomyoma. No malignancies were identified.
DISTAL PANCREATECTOMY FOR BENIGN AND LOW GRADE MALIGNANT TUMORS: SHORT TERM POSTOPERATIVE OUTCOMES OF SPLEEN PRESERVATION – A SYSTEMATIC REVIEW AND UPDATED META-ANALYSIS.

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\textsuperscript{1}Division of Surgical Oncology at Department of Surgery, \textsuperscript{2}Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine

BACKGROUND: The value of spleen preservation with distal pancreatectomy (DP) for benign and low grade malignant tumors remains unclear. The aim of this study was to evaluate the short term postoperative clinical outcomes in patients undergoing DP with splenectomy (DPS) or spleen preservation (SPDP).

METHOD: Online database search of PubMed, MEDLINE, EMBASE, SCOPUS, COCHRANE, and GOOGLE SCHOLAR was performed (2000 – Present); key bibliographies were reviewed. Studies comparing patients undergoing DP with either DPS or SPDP, and assessing postoperative complications were included. Relative risks with the corresponding 95% confidence intervals (CI) by random effects models of pooled data were calculated. Study quality was assessed using STROBE criteria.

RESULT: Out of 68 studies, 19 studies met our selection criteria. These included 1652 patients in total; 521 underwent SPDP while 1131 underwent DPS. Median age was 63 years. Meta-analysis of included data showed that there was no significant difference between the two groups in operative time. SPDP patients had significantly less operative blood loss (SMD -0.42; 95\% CI -0.78 to -0.07, P = 0.01), shorter duration of hospitalization (SMD -2.26, 95\% CI -3.74 to -0.79, p = 0.002), lower incidence of fluid collection and abscess (RR 0.69; 95\% CI 0.47 – 0.99; p = 0.04), lower incidence of postoperative splenic and portal vein thrombosis (RR=0.35; 95\% CI 0.22 – 0.57, p <0.001) and lower incidence of new onset postoperative diabetes (RR 2.10, 95\% CI 1.00 to -4.42, p = 0.05). For the whole group, there was no difference in incidence of post-operative pancreatic fistula (POPF) (RR=0.95; 95\% CI 0.65 – 1.40, P = 0.80), however, subgroup analysis of studies that used ISGPF criteria showed that DPS patients had increased rates of Grade B/C POPF (RR=1.35; 95\% CI 1.08 – 1.70, P = 0.01). All included studies reported 0\% 30-day mortality in both groups.

CONCLUSION: SPDP for benign and low grade malignant tumors is associated with shorter hospital stay and decreased morbidity compared to DPS.
CYTOREDUCTIVE SURGERY (CRS) AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC): CAN WE IMPROVE SURVIVAL WITH LESS POST-OPERATIVE COMPLICATIONS?

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Division of Surgical Oncology, Department of Surgery, University of Miami

BACKGROUND: CRS+HIPEC to treat peritoneal surface malignancies (PSM) is commonly associated with significant post-operative complications. The aim of this study was to determine predictors of survival and factors associated with post-operative complications in these patients.

METHODS: Records of all patients with PSM were retrospectively reviewed (Jan 2011-Aug 2015). Comorbidities, peritoneal cancer index (PCI), extent and margins of resections, operative time, estimated blood loss (EBL), ICU and length of hospital stay (LOS) were analyzed in uni- and multivariate models using Cox proportional hazards regression. Log-rank testing Kaplan-Meier curves were used to calculate overall survival (OS).

RESULTS: Eighty-five out of 142 patients with PSM were eligible for CRS+HIPEC, 11 of those were unresectable. Median age 54 years (23–74). Primary tumor sites were mostly in the appendix and colon (68%). Median operative time: 8.5 hours (4–13), median EBL: 500cc (150–2500). Median pre-operative PCI score was 14 (2–37). R0, R1 and R2 was achieved in 65%, 15%, and 20%, respectively. Number of organs resected was 1, 1-2 and ≥3 in 15%, 23% and 62%, respectively. Median ICU and LOS were 4 (0–52) and 8 days (1–88), respectively. 30-day mortality was 0%. Post-op complications included chemotherapy induced neutropenia (22%), surgical complications: fistula (7%), ileus and leak (5% each), intra-abdominal abscess and wound infection (4% each). R0 patients had the least morbidity (p<0.02) and wound infection rate (p<0.03) while R2 patients had the most pleural effusion (p<0.003). OS for CRS+HIPEC patients was 31 vs. 4 months in non CRS+HIPEC patients (p<0.01). Median OS was 35, 13 and 6 months for R0, R1 and R2 (p<0.01). Predictors of OS were pre and post-operative PCI (HR:1.05, p=0.01 and HR:1.07, p<0.01, respectively) on univariate analysis and LOS (HR:1.05, p<0.01) and abdominal wall implants (HR:3.98, p<0.01) on multivariate analysis.

CONCLUSION: Extensive CRS+HIPEC is achievable with low surgical complications. Patients with longer LOS and/or abdominal wall implants resection are more prone to early death. Resection margin is the most significant predictor of survival.
UNRESECTABLE HEPATOCELLULAR CARCINOMA: IS RADIOEMBOLIZATION AN ALTERNATIVE FOR CHEMOEMBOLIZATION?

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BACKGROUND: Transarterial Radio-embolization (TARE) has emerged as a newer regional technique to Transarterial Chemo-embolization (TACE) for treatment of unresectable hepatocellular carcinoma (HCC). The aim of this study is to evaluate clinical outcomes of both techniques.

METHODS: Online search for studies comparing TARE to TACE from 2005 to present was performed. Primary outcome was overall survival rate for up to 4 years. Secondary outcomes included post-treatment complications and treatment response. Quality of included studies was evaluated by STROBE criteria. Relative Risk (RR) and 95% Confidence Intervals (CI) were calculated from pooled data.

RESULTS: The search strategy yielded 172 studies, 5 met our selection criteria and included 653 patients undergoing embolization for unresectable HCC. Of these patients, 284 underwent TACE and 269 underwent TARE. Median age was 63 and 64 years for TACE and TARE, respectively. Meta-analysis showed no statistically significant difference in survival for up to 4 years between the two groups (HR=1.06; 95% CI: 0.81-1.46, p=0.567). TACE required at least one day of hospital stay compared to TARE which was mostly an outpatient procedure. TACE had more post-treatment pain than TARE (RR=1.96, 95% CI: 1.40-2.75, p<0.01), but less subjective fatigue (RR=0.62, 95% CI: 0.48-0.80, p<0.01). There was no difference between the two groups in the incidence of post-treatment nausea, vomiting, fever or other complications. In addition, there was no difference in partial or complete response rates between the two groups.

CONCLUSION: TARE appears to be a safe alternative treatment to TACE with similar complication profile and survival rates. Larger prospective randomized trials, focusing on patient-reported quality-of-life are required to consolidate these results, and to evaluate cost vs benefit for both techniques.
DOES ENUCLEATION OF PANCREATIC NEUROENDOCRINE TUMORS (PNETS) HAVE BETTER SHORT TERM OPERATIVE OUTCOMES THAN STANDARD RESECTION?

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BACKGROUND: The optimal extent of surgical resection of pNET remains unclear. The aim of this study was to objectively evaluate the short-term operative outcomes of enucleation vs. standard resection in these tumors.

METHODS: Online database search of PubMed, MEDLINE, EMBASE, SCOPUS, and COCHRANE was performed (2000-present). Studies evaluating outcomes of surgical resection in patients with both functional and nonfunctional pNET (nf-pNET) were reviewed. Pooled relative risk and corresponding 95% confidence interval (CI) by random and fixed effects models were calculated. STROBE criteria were used to assess study quality.

RESULTS: The search strategy yielded 15 articles that met our selection criteria (N=1035, 620 of which nf-pNET). 312 patients had enucleation while 664 patients had standard resection. Meta-analysis of all studies showed that the enucleation group had significantly shorter operative time (WMD= -95.6min, 95% CI -131.4 to -59.8, p<0.01), less operative blood loss (WMD= -172.6ml, 95% CI -340 to -5.1, p=0.04), yet higher overall incidence of post-operative pancreatic fistula (POPF) (RR= 2.08, 95% CI 1.39-3.12, p<0.01), and also higher incidence of clinically relevant POPF grades B/C (RR=1.32, 95% CI 0.98-1.77, p=0.07). There was no statistically significant difference between the two groups in length of hospital stay, post-operative hemorrhage, wound infection, and overall morbidity. Subgroup analysis of studies that included only nf-pNET patients showed similar trends to overall analysis.

CONCLUSION: Enucleation for pNETs is performed in shorter time with less blood loss yet with more incidence of POPF. Prospective trials are needed to accurately compare oncologic and long-term outcomes.
LONG-TERM SURVIVAL BASED ON PATHOLOGIC RESPONSE TO NEOADJUVANT THERAPY IN ESOPHAGEAL CANCER

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BACKGROUND: Neoadjuvant therapy has become the standard of care for patients with locally advanced esophageal cancer. The addition of radiation to neoadjuvant chemotherapy has been shown to significantly improve complete response rates, but has not been shown to improve survival. Complete (pCR) and partial (pPR) pathologic response to treatment have been identified as important prognostic markers for survival. The purpose of this study was to determine the long-term outcomes of patients receiving neoadjuvant chemotherapy alone (CA) compared with chemoradiation (CRT), stratified by pathologic response rates.

METHODS: Data from a prospectively maintained database of esophagectomies performed for cancer (1999 – 2012) was analyzed. 298 locally advanced esophageal cancer patients that underwent either neoadjuvant CA (n = 232) or CRT (n = 66) followed by esophagectomy were identified. Preoperative and pathologic staging were compared to assess treatment response. Overall survival (OS) was determined and compared using Kaplan-Meier statistics.

RESULTS: The pCR rate for patients in the CRT group was 27.3% compared to 11.7% in the CA group (p < 0.01, median follow-up: 49.5 vs. 64.4 months; respectively). There was no difference in the pPR rate between CRT (50%) and CA (49.6%). For patients with a pCR, 10-year OS was similar between the CA and CRT groups (74% vs. 64%). However, patients that had a pPR had significantly improved 10-year OS with CA (67%) as compared with CRT (34%, p < 0.002). When combining pCR and pPR, 10-year OS remained significantly greater in the CA group (69%) versus the CRT group (43%, p<0.003). CA patients that had a pPR had significantly improved OS compared with non-responders (pNR)(67% vs. 27%, p < 0.0001). Conversely, OS for CRT pPR patients was similar to pNRs (p = 0.45). (Figure)

CONCLUSION: Complete pathologic response after neoadjuvant therapy is a strong predictor of long-term OS. Neoadjuvant CA improves OS regardless of the degree of response, suggesting that response to chemotherapy in the primary tumor and lymph nodes may be a surrogate for control of systemic disease. The addition of radiation therapy enhances pCR rates but does not appear to improve OS compared with neoadjuvant CA alone.
INVASION OF RETE TESTIS, HILAR FAT, AND EPIDIDYMIS BY TESTICULAR MALIGNANT GERM CELL TUMORS DOES NOT JUSTIFY UPSTAGING TO PT2.

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\(^1\)University of Miami/Jackson Memorial Hospital, Pathology and \(^2\)Medical College of Wisconsin, Pathology, Milwaukee, WI, United States.

BACKGROUND: The significance of rete testis, hilar fat, or epididymis involvement by malignant germ cell tumors (MGCT) is controversial. AJCC cancer staging (7\(^{th}\) edition) classifies involvement of any of these structures as pT1, however, disagreement persists as to whether these findings, in the absence of vascular invasion, warrants a pT2 stage (PMID:25619976). Some studies suggest that rete testis involvement is associated with higher rate of metastasis (PMID: 23238629). A cohort of testicular MGCT were studied to clarify the significance of involvement of these structures in pathologic staging.

METHODS: We reviewed consecutive pT1 and pT2 orchiectomies with MGCTs performed between 2000-13 in 2 academic institutions. Standard grossing techniques were used. pT1 neoplasms were subdivided into those with involvement of rete testis, hilar fat, and/or epididymis (pT1-inv), and those without involvement (pT1 NO-inv). Correlation with recurrence/metastasis (RM) was assessed using Fisher’s, Anderson-Darling, and Kruskal-Wallis tests for statistical analysis.

RESULTS: Results are displayed in the table. Patients with pT1-inv do not demonstrate significant higher rate of RM than pT1 NO-inv (p=0.165). A trend to higher rate of RM in pT2 neoplasms compared to pT1-inv was identified (p=0.115).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>General (n=157)</th>
<th>Study group</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pT1 NO-inv (n=85)</td>
<td>pT1-inv (n=21)</td>
<td>pT2 (n=51)</td>
<td>p-value</td>
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<tr>
<td>Age, years</td>
<td>31 (32.9, 14-83)</td>
<td>30.5 (32.3, 16-62)</td>
<td>34 (35.3, 19-81)</td>
<td>31 (32.9, 14-83)</td>
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</tr>
<tr>
<td>Follow-up, months</td>
<td>50.7 (56.1, 2-180.4)</td>
<td>51.8 (59.5, 2.8-180.4)</td>
<td>55.5 (61.4, 39-100.4)</td>
<td>35 (48.3, 2-160)</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>Recurrence/Metastasis</td>
<td>55 (35%)</td>
<td>27 (32%)</td>
<td>5 (24%)</td>
<td>23 (45%)</td>
<td>0.165</td>
<td></td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Seminoma</td>
<td>81 (52%)</td>
<td>43 (51%)</td>
<td>14 (67%)</td>
<td>24 (47%)</td>
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<td></td>
</tr>
<tr>
<td>Embryonal</td>
<td>13 (8%)</td>
<td>4 (5%)</td>
<td>1 (5%)</td>
<td>8 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>61 (39%)</td>
<td>36 (42%)</td>
<td>6 (28%)</td>
<td>19 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>-</td>
<td>-</td>
<td></td>
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</tr>
</tbody>
</table>

Data in median (mean, range)

CONCLUSION: pT1 testicular MGCT with or without involvement of rete testis, hilar fat, and/or epididymis do not have a significant difference in rate of RM. Even though a trend is noted to have higher rate of RM in pT2 tumors in comparison to pT1 neoplasms with involvement of the structures, this was not significant. These data support current AJCC cancer staging guidelines, where involvement of rete testis, hilar fat, and/or epididymis by MGCT without vascular invasion is staged as pT1 neoplasm.
TREATMENT OF PEDIATRIC ABDOMINAL ANGIOSARCOMA WITH CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY: CASE REPORT AND REVIEW OF THE LITERATURE

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BACKGROUND: Angiosarcoma is a rare, but highly aggressive tumor arising from vascular endothelial cells, with a five-year overall survival rate of 35%. Peak incidence of abdominal angiosarcoma is in the seventh decade of life, and very few cases have been reported in the pediatric population. Due to the sparse literature regarding the management of pelvic angiosarcomas in the pediatric population, there are no formal guidelines for treatment at this time.

METHODS: We report the case of an adolescent girl who developed a pelvic epithelioid angiosarcoma treated with neoadjuvant chemotherapy, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). In addition, we conducted a systematic review of the current literature from 1990 to 2016 to investigate primary and secondary abdominopelvic angiosarcoma in the pediatric population and the effectiveness of treating angiosarcomas with CRS and HIPEC.

RESULTS: An adolescent girl presented with refractory malignant ascites. Imaging and diagnostic laparoscopy revealed a widely metastatic pelvic angiosarcoma that appeared to arise from the right ovary. The patient received one cycle of doxorubicin and cyclophosphamide, followed by four cycles of doxorubicin, ifosfamide and mesna, resulting in a partial response with resolution of ascites. The patient then underwent extensive CRS and HIPEC with mitomycin for 90 minutes. The patient tolerated the procedure well with no acute events postoperatively. Surgical pathology revealed foci of epithelioid angiosarcoma grade 3/3. Overall, 70% of the tumor appeared to show treatment effect and 30% was viable.

Our literature review demonstrated the efficacy of CRS with HIPEC in treatment of diffuse multifocal abdominal disease. CRS with HIPEC increases disease free survival (DFS) and overall survival (OS) in pediatric patients with peritoneal sarcomatosis. Pediatric patients who treated peritoneal cancer with HIPEC had a three year OS of 71%, compared to 26% and 62% with chemotherapy alone and surgery alone, respectively. Additionally, the only survivors at 3 years from time of diagnosis were those that had the addition of the HIPEC.

CONCLUSION: Even though there is no widely accepted standardized treatment regimen for abdominopelvic angiosarcomas in the pediatric population, the data suggests that CRS and HIPEC is a safe, reasonably tolerated treatment modality in pediatric patients with extensive abdominal metastasis. We propose the creation of a multi-institutional registry to evaluate the role of CRS and HIPEC in inducing remission of abdominopelvic angiosarcomas in the pediatric population.
PODOCYTE-SPECIFIC SMPDL3-B DEFICIENCY IS NECESSARY TO CAUSE RADIATION-INDUCED PODOCYTOPATHY

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2Peggy and Harold Katz Family Drug Discovery Center and Division of Nephrology, Department of Medicine, University of Miami
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BACKGROUND: The molecular mechanisms responsible for the development of proteinuria and glomerulosclerosis in radiation nephropathy remain largely unknown. Podocytes plasma membrane lipid raft has crucial Sphingolipids that plays a significant role in their proper function. Many glomerular disorders are characterized by foot processes effacement, mesangial expansion and loss of podocytes. Recently, sphingomyelin phosphodiesterase acid-like 3b (SMDPL3b) was identified as a lipid-associated enzyme, that regulates plasma membrane fluidity. Here we tested the hypothesis that SMPDL3b overexpression protects podocytes from radiation injury.

DESIGN/METHODS: Human podocytes were differentiated at 37 °C on collagen coated culture dishes for 14 days. Cells were pretreated with rituximab antibody then were radiated with a single dose of X-Ray radiation (8 Gy) for 4 min. SMPDL3b expression post radiation was determined by real time PCR (RT-PCR) and Western blotting. Sphingolipid metabolites were analyzed by mass spectrometry. Cytoskeletal remodeling and morphological changes were detected post radiation with phalloidin/ARP3 and phalloidin/ezrin staining using confocal microscopy. Methyl thiazol tetrazolium (MTT) assay was performed for determining cell viability.

RESULTS: After radiation injury, total cellular ceramide levels were elevated by 30% compared to baseline. In particular, C16:00, C24:00 and C24:1 ceramides were the most abundant ceramide species detected. SMPDL3b expression at protein level was dropped significantly however no significant changes were observed at transcriptional level. Interestingly, SMPDL3b overexpressing podocytes had higher basal levels of sphingosine-1 phosphate and maintained basal ceramide levels post irradiation. Morphologically, irradiated podocytes demonstrated loss of lamellipodia and remodeling of cortical actin. Furthermore, the actin binding protein ezrin in wild-type podocytes relocated from the plasma membrane to the cytosol as early as 2 hrs post radiation. In contrast, SMPDL3b overexpressing podocytes were protected from radiation-induced cytoskeletal remodeling. After 24 hours of radiation exposure, viability of wild-type podocytes decreased by 18.9 % whereas SMPDL3b overexpressing podocytes displayed radio resistance. Rituximab pretreatment protects podocyte function and cytoskeletal remodeling post radiation injury.

CONCLUSION: This study highlighted the importance of sphingolipids in podocyte function. We investigated that podocyte-specific SMPD13-b deficiency is necessary to cause radiation-induced nephropathy and rituximab could act as a direct modulator of podocyte function in an SMPDL3-b dependent manner.
A PATIENT-SPECIFIC EX VIVO SCREENING PLATFORM FOR PERSONALIZED ACUTE MYELOID LEUKEMIA THERAPY


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BACKGROUND - Acute Myeloid Leukemia (AML) is a diverse disease that is fatal in the majority of patients. For younger patients fit enough to tolerate standard chemotherapy, only 20% of patients achieve long term survival due to high relapse rates. For older patients unfit for intensive therapy, mortality is close to 100%. The cornerstone of AML induction regimens consist of a nucleoside analog (cytarabine) combined with an anthracycline (so called “3+7” regimens). Three problems exist with this approach: 1) 3+7 regimens have remained unchanged for the last four decades, 2) mortality rises steeply with age and 3) a “one size fits all” approach is not appropriate for such a genetically diverse disease. Here, we address all three problems by applying a personalized approach for individual patients, selecting drugs from a library of clinically approved compounds to offer patients the safest possible chance of achieving remission and ultimately cure of their disease.

METHODS - In this proof-of-principle study, we optimized an ex vivo high-throughput drug screening platform measuring AML cell survival after exposure to over 200 U.S. FDA approved oncology drugs. This multiplex assay is designed for individual AML patients and tests agents over a 10,000-fold concentration range. We screened patient derived blasts against normal bone marrow mononuclear cells to identify the most effective leukemia selective agents. To compliment this functional ex-vivo screen, we employed a genomics approach using predictive simulation software to generate patient specific avatars, which map individual dysregulated and interconnecting signaling pathways.

RESULTS – Through phenotype screening of primary cells collected from a highly refractory AML patient (patient # PD001), our ex-vivo assay identified a list of drugs based on their ability to effectively and selectively reduce the viability of the patient’s leukemic blasts vs. normal bone marrow mononuclear cells. The patient specific avatar generated for patient PD001 identified a series of dysregulated pathways converging on cell proliferation and viability. Both functional and genomic approaches identified the tyrosine kinase ponatinib, as a potentially relevant clinical candidate. Potentially effective combination approaches were also predicted (eg ponatinib with rosuvastatin, ponatinib with decitabine). Since our ex vivo assay identified Bortezomib as a clinical candidate and since we successfully negotiated off-label use of this agent, we selected Bortezomib for a therapeutic trial in patient PD001. After three doses of Velcade at 1.5 mg/m2 (Days 1, 4 and 8), serial blood counts revealed a dramatic fall in total white count and circulating blasts (96% to 20%) This is noteworthy since Bortezomib as a single agent is generally not capable of producing clinically meaningful responses when used for patients with heavily pre-treated and refractory disease.

CONCLUSIONS– Our study justifies continued development of this novel, iterative functional/genomics approach to personalized therapeutics in AML. Our model identifies candidate drugs that can be readily re-purposed for immediate clinical use, whilst at the same time providing insights into underlying mechanism of action, informing on rationally designed combination strategies and biomarker candidates.
RACIAL/ETHNIC DISPARITIES OF OBESITY IN A BREAST CLINIC POPULATION: CONSIDERATION FOR A WEIGHT LOSS PROGRAM IN IMPROVING CLINICAL OUTCOMES

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BACKGROUND: Accumulating evidence suggest that obesity is associated with breast cancer diagnosis, recurrence, and mortality. Obese subjects with genetic predisposition may need more aggressive weight loss management, such as bariatric surgery. Therefore, the primary aim of this study was to assess the racial/ethnic disparities in obesity and the prevalence of breast cancer study participants who may be eligible for bariatric surgery.

DESIGN/METHODS: In three clinic-based studies conducted at University of Miami during 2008 to 2015, we evaluated 462 healthy controls and 975 breast cancer patients. Genotyping data of two obesity-related genes (FTO and MC4R) were also evaluated. Race/ethnicity and obesity-related comorbidities were self-reported. Body Mass Index (BMI) was calculated as kg/m². The classification of BMI was: (1) < 18.5, underweight; (2) 18.5–24.9, normal weight; (3) 25.0–29.9, overweight; (4) 30.0–34.9, class I obesity; (5) 35.0–39.9, class II obesity; and (6) ≥ 40.0, class III obesity. The NIH eligibility for bariatric surgery was for class II obese subjects with obesity-related comorbidities and class III obese subjects.

RESULTS: The study consists of 70.0% Hispanic whites (HW), 21.7% black or African American (AA), and 6.4% non-Hispanic whites (NHW). Mean and SD of age was 54.1± 9.9 years and mean BMI was 29.0±6.1 kg/m². Overall, about 11.1% of study participants met criteria for bariatric surgery and there were significant racial/ethnic disparities (19.7% AA, 8.5% HW, 8.8% NHW, and 17.2% others; p<0.0001). Subgroup analysis observed increased BMI at follow up (29.60 vs. 29.16 kg/m², p=0.00229). Women with the AA risk genotype of rs1121980 (FTO gene) had 3.6-fold higher risk of obesity class II or III compared to those with the GG genotype (p=0.00393).

CONCLUSION: In addition to cancer risk, obesity is a major risk factor for cancer treatment-related side effects and worse survival. Our results suggest that at least 11% of breast cancer patients may be eligible for bariatric surgery. Considering some other beneficial effects of bariatric surgery on physical quality of life, metabolic syndrome, diabetes, and microbiome, future studies will consider weight loss and bariatric surgery programs in breast cancer patients, particularly in underserved minorities with higher obesity rate and worse survival.
ARGINYLASTION AS A NOVEL REGULATOR OF PROSTATE CANCER PROGRESSION

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Molecular and Cellular Pharmacology, University of Miami

BACKGROUND: In this study, we evaluate the role of post-translational arginylation in prostate cancer, and introduce its potential as a biomarker of prostate cancer progression. Arginylation has not yet been studied in cancer. Our lab has observed Aringyltransferase (Ate1) is required for oxidative stress-mediated apoptosis. Our preliminary data in multiple eukaryotic cell models demonstrate that a downregulation of Ate1 increases resistance to oxidative stress, and elevated Ate1 is sufficient to induce cell death. Preliminary data mining shows that a downregulation of Ate1 correlates with a poorer prognosis in prostate cancer. Because prostate cancer cells produce a high amount of oxidative stress, the decrease of Ate1 likely increases their survival. We hypothesize that Ate1 is essential for the normal cellular response to insurmountable oxidative stress leading to apoptosis, and that a downregulation of Ate1 will promote cancer cell progression.

DESIGN/METHODS: We found that a loss of Ate1 in a nontumorigenic fibroblast cell line promotes spontaneous tumorigenicity within immunocompromised mice, a disruption of normal cell-cell interactions, and loss of contact inhibition. Also consistent with our hypothesis, prostate cancer cell line PC-3 with stably knocked down Ate1 exhibit higher invasiveness in the Boyden Chamber invasion assay, and higher resistance to H$_2$O$_2$-induced cell death during a 12-hour variable dose treatment. Similarly, the highly metastatic subpopulation of PC-3, PC3-ML, has naturally reduced Ate1 and exhibits higher invasiveness and resistance to H$_2$O$_2$. Finally, histological analysis of primary patient prostate cancer samples show a dramatic reduction of Ate1 compared to normal prostate tissue.

RESULTS: A loss of Ate1 is positively correlated to an increase in metastatic phenotypes in vitro and in vivo. Preliminary studies in vitro suggest that a loss of Ate1 is a driver of metastasis.

CONCLUSION: Our findings warrant further study of Ate1 as a metastasis suppressor, as well as a potential biomarker for prostate cancer progression.
TRANSLATIONAL RESEARCH

Abstract #56

COMPARISON OF MALIGNANCY RATES IN THYROID FINE NEEDLE ASPIRATION USING THE BETHESDA SYSTEM IN A TERTIARY CARE CENTER AND A COMPREHENSIVE CANCER CENTER: INSTITUTIONAL STATISTICS

Victor Delacruz MD, Claudia P Rojas MD, Elvia Goez-Gutierrez MD, Carmen Gomez-Fernandez MD, Merce Jorda MD, PhD, MBA, Monica Garcia-Buitrago MD.

Department Pathology and Laboratory Medicine, University of Miami, Jackson Memorial Hospital

BACKGROUND: The Bethesda System for reporting Thyroid Cytopathology is the standard for interpreting Fine Needle Aspiration (FNA) specimens. This system recommends six diagnostic categories. Each category implies a risk of malignancy and a recommended clinical management. Our objective was to determine the rate of malignancy for categories III to VI thyroid nodule FNAs in our comprehensive cancer center and our tertiary care academic hospital.

DESIGN/METHODS: We performed a retrospective review of thyroid cytology FNA specimens with concomitant thyroid resections collected from 2013 to 2015 at our tertiary care academic hospital (TCAH) and comprehensive cancer center (CCC). Cases classified as Atypia/Follicular Lesion of Undetermined Significance (AUS/FLUS, Bethesda III), Suspicious for Follicular Neoplasm (Bethesda IV), Suspicious for Malignancy (Bethesda V), and Malignant (Bethesda VI) were included. Occult / incidental microcarcinomas were excluded from this analysis.

RESULTS: Of the 1343 patients with FNA from thyroid nodules, 156 patients had surgical resections (125 females, 31 males) with concurrent 202 FNAs. The mean age was 50 years (range 14 to 80 y/o). AUS/FLUS represented 38% (77/202), Suspicious for Follicular Neoplasm, 7% (15/202), (Fig 1A and 1B); Suspicious for Malignancy, 10% (21/202), (Fig 2A); and Malignant cases, 25% (50/202), (Fig 2B, 3A, and 3B). Malignancy rates at the TCAH and CCC were as follows: Bethesda III, 20% and 40%; Bethesda IV, 36% and 0%; Bethesda V, 100% and 95%; and Bethesda VI, 100% and 100% respectively (Table 1). Most malignant surgical specimens diagnosed as Category III nodules were papillary thyroid carcinomas, follicular variant.

CONCLUSION: The malignancy rates for Bethesda III (AUS/FLUS) thyroid nodules in our institutions (20% and 40%) are higher than what has been generally proposed for this category (5%-15%). This higher rate is more evident in the patients seen at our referral comprehensive cancer center. Individual institutional malignancy rates need to be estimated at every laboratory or hospital setting.

Table 1. Rate of Malignancy at a Tertiary Care Academic Hospital and a Comprehensive Cancer Center by Bethesda Category

<table>
<thead>
<tr>
<th>Bethesda Category</th>
<th>Malignancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertiary Hospital</td>
</tr>
<tr>
<td>III (AUS/FLUS)</td>
<td>30 (30%)</td>
</tr>
<tr>
<td>IV (Suspicious for follicular neoplasm)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>V (Suspicious for malignancy)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>VI (Malignant)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
</tr>
</tbody>
</table>
PRMT4 AS A THERAPEUTIC TARGET IN AML

S. Greenblatt, PJ Hamard, G. Cheng, T. Asai, E. Blumenthal, F. Liu, S. Nimer; Sylvester Cancer Center, University of Miami

BACKGROUND: Acute myeloid leukemia (AML) is an aggressive and lethal disease characterized by the accumulation of immature blood cells in the bone marrow. Although survival rates for AML have increased over the past few decades, only 10% of patients over the age of 60 will be cured by these treatments. Of these patients, over 75% will relapse, and 5-15% will die due to treatment related side effects. Specific fusion proteins found in AML have been shown to be dependent on epigenetic modifying enzymes and susceptible to chemical inhibition. Translating these discoveries into novel targeted therapies for AML will improve survival rates and decrease treatment-related mortality. Our lab has recently shown that the epigenetic enzyme PRMT4 is significantly overexpressed in AML. PRMT4 catalyzes the formation of asymmetric dimethyl arginine on histone substrates, such as H3R17 and H3R26, and on transcriptional regulators such as p300 and RUNX1. We have shown that overexpression of PRMT4 blocks the myeloid differentiation of human hematopoietic stem and progenitor cells (HSPCs), whereas its knockdown induces their myeloid differentiation. Still, the function and mechanism of action of PRMT4 in normal and malignant hematopoiesis remains largely unknown.

DESIGN/METHODS: We generated PRMT4-targeted shRNA, and conditional knockout mice to study how modulation of PRMT4 affects leukemia cell biology. Leukemia cell lines with KD of PRMT4 were evaluated for changes in cell proliferation, cell cycle progression, and differentiation. We used small molecule PRMT4 inhibitors in leukemia cell lines and primary AML samples established at the University of Miami. The PRMT4 specific histone marks H3R17me and H3R26me and its non-histone substrates, such as RUNX1, were measured by western blot. The induction of differentiation or apoptosis was compared to normal human CD34+ stem/progenitor cells.

RESULTS: Knockout of PRMT4 in the hematopoietic system completely abrogated the development of leukemia in an MLL-AF9 or AE9a driven model system. Knockdown of PRMT4 resulted in increased apoptosis, decreased proliferation, and increased differentiation in AML cell lines. RNA sequencing analysis identified defects in cell cycle progression and decreased transcriptional activation of E2F and Myc target genes. Our preliminary data suggests that pharmacologic PRMT4 inhibition prevents leukemic cell growth at an IC50 in the low micro-molar range in a panel of leukemia cell lines. Additionally, PRMT4 inhibition induces differentiation and apoptosis in AML cells but is less toxic to normal CD34+ controls.

CONCLUSION: Our data supports the hypothesis that PRMT4 functions as an oncogene in human AML, and that targeting PRMT4 could represent an effective and novel “epigenetic-targeted” strategy for treating leukemia.
A NOVEL CK1d/BRD4 PATHWAY FOR THE TREATMENT OF MEDULLOBLASTOMA

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BACKGROUND: Medulloblastoma is the most common malignant pediatric brain tumor with variable prognosis due to its clinical and genomic heterogeneity (Mueller and Chang, 2009; Robinson et al., 2012). Despite recent treatment advances, approximately 40% of children experience tumor recurrence, and 30% will die from this disease. Therefore there is a need to develop novel therapies for patients. Recently, we observed that Casein kinase 1d (CK1d), may be an attractive therapeutic target for medulloblastoma. CK1d is a serine/threonine kinase that controls cell cycle progression, signal transduction and neurogenesis. We found high levels of CK1d protein in mouse models of medulloblastoma (Penas et al., 2015). Furthermore, CK1d inhibition dramatically reduced medulloblastoma tumor growth. In addition, we have recently found that CK1d phosphorylates the epigenetic reader bromodomain-containing protein 4 (BRD4). BRD4 is a therapeutic target in several cancers, including medulloblastoma. However, resistance to BRD4 inhibitors has been described. We hypothesize that dual inhibition of CK1d and BRD4 may reduce the observed resistance and thereby reduce medulloblastoma progression.

DESIGN/METHODS: We used granule progenitor cells and medulloblastoma Ptch^-/-;P53^-/- mouse cells to determine the effects of CK1d phosphorylation of BRD4. Cells were incubated with the CK1d inhibitor SR-1277 and the phosphorylation levels of BRD4 were determined by WB and its binding to chromatin by ChIP. We also combined BRD4 and CK1d inhibitors (JQ1 and SR-1277, respectively) and analysed Gli1 mRNA expression to determine synergistic effects.

RESULTS: Treatment with SR-1277 reduced BRD4 phosphorylation confirming that CK1d phosphorylates BRD4. Consistent with a functional interaction between CK1d and BRD4, we found that BRD4 association with the proximal promoter region of the Gli1 locus can be inhibited by either the CK1d inhibitor SR-1277 or the BET inhibitor I-BET151. In addition, both CK1d and BET inhibition reduced Gli1 mRNA levels in mouse Ptch1^+/^-;Trp53^-/- medulloblastoma cells when we used the brain penetrant inhibitors JQ1 and SR-1277. We also found synergy by combining these compounds.

CONCLUSION: Collectively, our studies validate the CK1d-BRD4 pathway as a novel target in medulloblastoma. The importance of our work is underscored by the possibility that simultaneous inhibition of CK1d and BRD4 could overcome the resistance observed with BRD4 inhibitors. There are two major mechanisms of BET inhibition resistance described. First, BRD4 becomes hyperphosphorylated, which promotes binding to chromatin independently of the bromodomain pockets, and therefore BET inhibitors do not affect chromatin binding. Second, BRD4 inhibition enhances MYC expression through the WNT pathway. Since CK1d inhibition decreases BRD4 phosphorylation and signaling via the WNT pathway, it is feasible that combinatorial therapy may reduce BET resistance and therefore enhance the therapeutic benefits to patients.
PRECLINICAL ASSESSMENT OF THE NATURAL COMPOUND ELATOL AS A NOVEL eIF4A INHIBITOR FOR CANCER THERAPEUTICS

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BACKGROUND: Targeted signaling inhibitors have failed to revolutionize the care of most cancers because of redundant pathways that are easily co-opted to maintain survival. A key survival output at which multiple oncogenic signals converge is activation of cap-dependent translation, carried out by the eIF4F translation-initiation complex. Interference with this complex either genetically or pharmacologically shows potent preclinical activity against multiple cancer types. In particular, the DEAD-box RNA helicase and complex subunit eIF4A, necessary to unwind secondary structures found in the 5-UTRs of many oncogenes’ mRNAs, is a highly promising drug target. Several natural compounds that interfere eIF4A show potent tumorcidal activities in preclinical systems, but no such drug has entered or is scheduled to enter clinical evaluation. Problems that have plagued development of these compounds include difficult chemical synthesis, poor understanding of their true anti-neoplastic mechanisms, and resistance mediated by drug-efflux pumps. A small-molecule inhibitor with simpler chemical structure and clearer mode of interaction with eIF4A has potential to advance therapy for an array of human malignancies.

DESIGN/METHODS: We used a malachite green assay to screen a collection of natural compounds for ability to block the ATPase activity of eIF4A in vitro. We then assessed the mechanism and anticancer properties of our top hit, as well as its tolerance in vivo.

RESULTS: Six compounds emerged from the screen, of which four were found to be specific for this target, showing no activity in vitro against other DEAD-box helicase family members or other similar enzymes. Of these four, one, the marine-derived compound elatol, was found to cross cell membranes and potently promote toxicity against tumor cell lines derived from multiple different tumor types. Importantly, elatol has a significantly less complex chemical structure than other eIF4A inhibitors identified to date and is more easily synthesized in large quantities. We find elatol promotes loss of cap-dependent translational activation as indicated by diminished O-propargyl-puromycin incorporation in treated cells and specific loss of translationally regulated oncoproteins, including c-MYC, MCL1, and CYCLIN D3. We find elatol interacts with eIF4A at two key residues, blocking its binding to ATP, but had no activity in a screen of 97 oncogenic kinases, highlighting the specificity of its activity. We have established the maximum tolerated dose (MTD) in severe combined immunodeficient (SCID) mice to be 20mg/kg daily, and will use this to evaluate elatol’s anti-tumor activity in both xenograft and genetic mouse models.

CONCLUSION: Elatol is a novel inhibitor of cap-dependent protein translation and demonstrates promise toward an early drug-development program aimed ultimately at bringing the potential of anti-eIF4A therapy to the cancer clinic for the first time.
ATYPICAL ANTIPSYCHOTICS FOR THE TREATMENT OF BRAIN TUMORS

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BACKGROUND: Brain tumors are some of the most difficult types of cancers to treat in part due to the paucity of effective therapies able to cross the blood brain barrier. Drug “repositioning” is an attractive idea because the use of existing FDA-approved drugs can bypass or shorten critical steps of drug development. Antipsychotic drugs (APDs), both typical and atypical, are primarily used for the treatment of schizophrenia and mood disorders. However, they may also have potential as treatments for CNS cancers. Compared to typical APDs, atypical APDs may be especially suitable for this purpose due to the lower frequency of extrapyramidal side effects (EPS), while also causing side effects that may actually benefit patients suffering from cancer. A primary side effect of APDs is metabolic disturbance resulting in weight gain. Along with reduced nausea often experienced by patients treated with atypical APDs, these effects may actually benefit cancer patients undergoing radio and chemotherapy. In addition, CNS cancer patients often experience depression and other psychiatric symptoms that may be reduced or eliminated with the use of atypical APDs. Quetiapine, in particular, is well known for effectively treating depression and mood disturbances. Furthermore, recent data suggests that these drugs may possess anti-cancer effects. APDs have been shown to induce growth inhibition in lymphoma, neuroblastoma, non-small cell lung cancer and leukemia as well as potentiate the effects of some commonly used chemotherapeutic agents in leukemia. Here we sought to investigate the effects of clozapine, risperidone, and quetiapine on brain tumor cell lines.

DESIGN/METHODS: Anti-cancer effects of APDs on Medulloblastoma (DAOY) and glioblastoma cell lines (U87), including patient-derived glioblastoma stem cells (GSCs). Viability was determined using MTS assay. Cells were exposed to increasing concentrations (10-100uM) for 72 hr or (0.5-10uM) for 144 hr. Effects on cell signaling pathways was evaluated by western blot analysis.

RESULTS: All 3 APDs induced dose-dependent brain tumor cell death at 72 hr treatment, with clozapine being the most effective. However these concentrations are not clinically achievable, therefore we exposed the cells to lower doses 5-25uM for 6 days. Surprisingly these concentrations of clozapine had no effect on cell viability while both risperidone and quetiapine reduced cell viability. We then sought to determine the effects of risperidone and quetiapine on patient-derived glioblastoma stem-like cells (GSC’S). At 6 days of treatment 10uM of risperidone or quetiapine reduced GSC viability to < 50%. While lower doses of risperidone failed to reduce GSC viability, quetiapine reduced viability by 15% at concentrations as low as 500nM.

CONCLUSION: Patients suffering from brain tumors often experience a myriad of symptoms including nausea, loss of appetite and psychiatric aspects. APD’s such as quetiapine may not only improve the quality of life but may also negatively affect tumor growth. Here we demonstrated that clinically relevant concentrations of quetiapine reduce GSC viability. Ongoing experiments will evaluate the molecular mechanisms of APD’s on these and examine the potential of combining APD’s with the current standard of care.
IMPROVING CERVICAL CANCER SCREENING AMONG TRANSGENDER MEN

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BACKGROUND: Transgender men, or individuals assigned female sex at birth who self-identify as men, experience significant health disparities, and may be at excess risk of developing and dying of cervical cancer. In large part, this disparity reflects lack of access to, and underutilization of, routine screening. Relative to non-transgender women, transgender men are less likely to receive Pap smears once every three years, as recommended by national guidelines. Lack of health insurance, limited access to care, perceived discrimination, and emotional distress related to undergoing a Pap smear likely preclude screening uptake within this vulnerable population sub-group. Such barriers are likely exacerbated by the limited efficacy of Pap smears/cytology in transgender men undergoing testosterone therapy for gender transitioning. We conducted formative mixed-methods (rapid assessment survey and focus groups) research to understand experiences with cervical cancer screening among transgender men, as well as perceptions of potential alternative forms of screening such as HPV self-sampling.

DESIGN/METHODS: We conducted an anonymous rapid assessment survey with 24 transgender men between the ages of 21 and 65 to measure previous experiences with healthcare overall and cervical cancer screening, as well as cervical cancer screening preferences. The survey was administered both in-person and online. Data were entered into REDCap. We also conducted three qualitative focus groups with seven transgender men between the ages of 21 and 65 to elucidate barriers to, and facilitators of, cervical cancer screening.

RESULTS: Results from the survey indicate that approximately half of these men were either unscreened or underscreened for cervical cancer. Moreover, when given a description of the HPV self-sampling process, these men almost unanimously (80%) indicated a preference for HPV self-sampling over Pap smear for cervical cancer screening. The majority (63%) of men surveyed also indicated that they had previously had to teach healthcare providers about transgender people in order to receive appropriate care, indicating a significant need for trans-competent providers in the cervical cancer screening process. Barriers to screening elucidated by the qualitative focus groups included: lack of knowledge about cervical cancer and the need for screening, lack of insurance/access, gender dysphoria and emotional discomfort with the Pap smear, OB/GYN offices are women’s spaces, and stigma/discrimination from healthcare providers, staff, and patients. Facilitators of screening included: trans-competent healthcare providers and staff, believing the screening is important, trans-friendly office environment, and low-cost screening options. All focus group participants were enthusiastic about and preferred HPV self-sampling as an option for cervical cancer screening.

CONCLUSION: Our mixed-methods formative work elucidated many barriers to traditional cervical cancer screening above and beyond limited knowledge and access. In addition to increasing knowledge and access, as well as providing trans-friendly spaces and trans-competent healthcare providers, HPV self-sampling may improve cervical cancer screening uptake among transgender men. Given our results, we have applied for R21, K99/R00, and an internal UM grant to both pilot and formally test HPV self-sampling as a cervical cancer screening strategy among transgender men.
AN INTEGRATED MULTI-MODALITY IMAGING AND RADIATION PLATFORM FOR CANCER RESEARCH

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BACKGROUND: X-ray CT is invaluable for imaging anatomy and guiding focal radiation. Bioluminescence and fluorescence imaging are favorable for functional imaging of live cancer cells at molecular levels. We have developed a multiplex X-ray/bioluminescence/fluorescence tomography system integrated with previously constructed image guided Small Animal Arc Radiation Treatment System (iSMAART).

METHODS: The iSMAART platform consists of a stationary X-ray tube, a flat-panel detector, an animal stage and a customized X-ray collimation subsystem providing CT guided radiation. A CCD camera coupled with a high speed lens was utilized to collect bioluminescence and fluorescence signals. X-ray CT provide animal anatomy and accurate surface contour used to construct mice model for bioluminescence tomography (BLT) and fluorescence molecular tomography (FMT) reconstruction. In vivo animal experiments with orthotopic prostate tumor model were carried out to evaluate the performance of the BLT imaging system. Iodinated contrast CT was performed to delineate contrast enhanced tumors and served as a benchmark against BLT. Preliminary studies were carried out on one mouse with surgically implanted indocyanine green (ICG) loaded glass tube, to evaluate the performance of the FMT imaging system.

RESULTS:

![3D rendering of BLT and CT](image1)

**Figure 1.** In the 3D volume rendering, BLT reconstructed tumor volume is fused with the CT bony anatomy. BLT is overlaid on top of contrast CT in the three orthogonal slices. White dashed contour indicates the tumor boundary outlined from the contrast CT. Good agreement between BLT and CT demonstrates the high performance of BLT in terms of both tumor location and tumor volume.

![3D rendering of FMT result](image2)

**Figure 2.** FMT results for the in vivo mouse experiment with implanted ICG tube. Through strictly registering the torso contour in FMT and CT, the high contrast glass tube in CT can provide accurate reference to evaluate the performance of FMT. The fused 3D volume rendering demonstrates that the FMT-reconstructed fluorescence target matches well with the ICG tube identified from CT.

CONCLUSIONS: The BLT and FMT systems can accurately differentiate and localize tumors marked with bioluminescence/fluorescence probes, together with X-ray CT, will provide accurate tumor assessment and precision radiation guidance in translational cancer research.
COMPUTATIONAL APPROACHES FOR IDENTIFYING THERAPEUTIC COMBINATIONS IN GLIOMA

Vasileios Stathias¹, Michele Forlin¹, Bryce Allen¹, Jennifer Clarke², Stephan Schürer¹, Nagi G. Ayad¹

¹University of Miami, Miami, FL  ²University of Nebraska, Lincoln, NE

BACKGROUND: Glioblastoma is the most common and aggressive malignant brain tumor. Despite medical advances in the field, the median survival time is still below 2 years since recurrence is nearly universal. Thus, the discovery of novel and specific molecular targets is needed.

DESIGN/METHODS: The purpose of this study is to leverage the large number of perturbation signatures from the NIH Library of Integrative Network-based Cellular Signatures (LINCS) and integrate them with patient data from The Cancer Genome Atlas (TCGA) and PubChem bioactivity data in an effort to prioritize compounds based on their synergistic effect in cancer treatment.

RESULTS: From the large number of LINCS L1000 transcriptional data capturing cellular responses after chemical or genetic perturbations, we extracted gene expression signatures that were indicative of specific LINCS compounds. Moreover, we compared the L1000 transcriptional profiles with ones from TCGA in order to identify characteristic signatures of major cancer types and prioritized small molecule compounds with discordant expression profiles to those cancer types. We then linked the above compounds to protein target annotations and therefore produced a compound-specific protein target profile. For this, we utilized biochemical data produced by the LINCS KinomeScan and KiNative assays and also biochemical data obtained through PubChem. Using the above information, we obtained pairs of compounds that may inhibit unlinked gene sub-networks that were produced through processing of TCGA transcriptional data.

CONCLUSION: The above process can be utilized to identify compound combinations towards specific cancer types and to prioritize the development of compounds with targeted polypharmacology.
TRANSLATIONAL RESEARCH

Abstract #64

MOLECULAR CHARACTERIZATION OF LACRIMAL GLAND ADENOID CYSTIC CARCINOMA

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1 Dr. Nasser Ibrahim Al-Rashid Orbital Vision Research Center, Bascom Palmer Eye Institute; 2 John P. Hussman Institute for Human Genomics, Sylvester Comprehensive Cancer Center, Dr. John T. Macdonald Foundation Department of Human Genetics; 3 Bascom Palmer Eye Institute, Molecular Oncology Research Program, Department of Surgery, 4 University of Miami Miller School of Medicine, Miami, FL.

BACKGROUND: Lacrimal gland adenoid cystic carcinoma (LGACC) is a rare but devastating form of orbital cancer. After initial control of surgery and chemo therapy, LGACC has high rates of local recurrence, chemo resistance and distant metastases, which is the main cause of cancer death. Currently, lack of cell or animal models greatly hinders the research on LGACC.

DESIGN/METHODS: We are aiming to establish LGACC cell lines from primary tumor. By injecting cells into NSG mice, we try to generate a mouse xenograft model for human LGACC. By western blot and immunohistochemistry (IHC), cell identity and proliferation markers are characterized in LGACC cell lines and tumors. Using proteomic screening, we are seeking to identify the differentially expressed proteins related to chemo resistance.

RESULTS: Three LGACC cells lines have been successfully generated. A novel mouse xenograft model highly mimicking the human LGACC has already been established. We have identified two potential cancer driving transcriptional factors, Notch1 and Myb highly expressed in LGACC cell lines and tumors. From the whole genome exon sequencing, we have identified genetic mutations of Notch1 can increase its transcriptional activities by luciferase assay. Meanwhile, we have identified FGF receptor 1 is induced upon chemotherapy which might lead to chemo resistance. Treatment of FGFR1 inhibitor can greatly reduce the proliferation of LGACC cell lines.

CONCLUSION: We have established cell and animal model for LGACC. Using genetic and proteomic profiling, we have characterized the molecular signatures of LGACC. We have identified two potential druggable targets for LGACC: FGFR1 and Notch1.
Targeting Androgen Receptor & Vitamin D Receptor in Triple Negative Breast Cancer

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**BACKGROUND:** Anti-estrogen and anti-HER2 treatments have been among the first and most successful examples of targeted-therapy for breast cancer. However, the treatment of Triple Negative Breast Cancer (TNBC) that lack estrogen receptor (ER) expression or HER2 amplification remains a major challenge. We previously discovered that approximately two-thirds of TNBCs express Vitamin D Receptor (VDR) and/or Androgen Receptor (AR) and hypothesized that TNBCs co-expressing AR and VDR (HR2-av TNBC) could be treated by targeting both of these hormone receptors.

**DESIGN/METHODS:** To evaluate the feasibility of VDR/AR-targeted therapy in TNBC, we characterized 15 different breast cancer lines and identified two HR2-av TNBC lines and examined the changes in their phenotype, viability and proliferation after VDR and AR targeted treatment.

**RESULTS:** Treatment of breast cancer cell lines with VDR or AR agonists inhibited cell viability in a receptor dependent manner and their combination appeared to inhibit cell viability additively. Moreover, cell viability was further decreased when AR/VDR agonist hormones were combined with chemotherapeutic drugs. The mechanisms of inhibition by AR/VDR agonist hormones included cell cycle arrest and apoptosis in TNBC cell lines. In addition, AR/VDR agonist hormones induced differentiation and inhibited cancer stem cells (CSCs) measured by reduction in tumorsphere formation efficiency, ALDH activity and CSC markers. Surprisingly, we found that AR-antagonist inhibited proliferation of most breast cancer cell lines in an AR-independent manner, raising questions regarding their mechanism of action.

**CONCLUSION:** AR/VDR targeted agonist hormone therapy can inhibit HR2-av TNBC through multiple mechanisms in a receptor dependent manner and can be combined with chemotherapy.
MARKED IN SITU DONOR FoxP3+CD4+ Treg EXPANSION VIA THE IL-2/CD25 AND TL1A/TNFRSF25 PATHWAYS AMELIORATES GVHD BUT PRESERVES ANTI-TUMOR RESPONSES IN RECIPIENTS POST-TRANSPLANT (HSCT)

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1Sylvester Comprehensive Cancer Center; 2Microbiology & Immunology; 3Medicine; 4Ophthalmology; University of Miami, Miller School of Medicine

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important therapeutic application for treatment of hematological malignancies, and is associated with a graft versus tumor (GVT) effect. Regulation of GVHD is critical for favorable HSCT outcomes. FoxP3+ regulatory T cells (Treg) are promising regulators of GVHD. Since donor Treg numbers needed for maximal efficacy are high and ex vivo expansion presents practical and scientific challenges, strategies to manipulate the compartment in situ would represent a significant therapeutic advance for HSCT recipients.

The Treg surface receptors TNF receptor super family 25 (TNFRSF25) and CD25 (IL-2Rα) can mediate Treg expansion following ligand binding. We recently developed a novel one week combination approach to expand functional Tregs in vivo by targeting these two receptors, using a fusion protein (TL1A-Ig) and low dose IL-2. The resulting Treg expansion is 100% higher compared to either reagent alone (5-7 fold vs. 2-3 fold, respectively). Notably, the expansion is transient and there are no long-term complications as assessed by blood counts, immune phenotype/function and tissue pathology 6 months following cessation of treatment. Interestingly, we noted a significant gender disparity as Treg expansion was higher in female vs. male animals.

Next, we wanted to compare the Treg expansion protocol to the current clinical use of post-transplant cyclophosphamide for GVHD prophylaxis. We have developed both MHC-mismatched (B6→BALB/c) and MHC-matched (B10.D2→BALB/c) pre-clinical allo-HSCT transplant models using high-dose PTC (Day +3/+4) for GVHD prophylaxis. Both strategies markedly decreased clinical GVHD and improved survival. Notably, less weight loss was observed immediately post-HSCT and during the first 2 weeks in recipients of Treg expanded donors. Three weeks post-HSCT, recipients of expanded Tregs exhibited less thymic damage including a normal SP/DP phenotype consistent with the higher level of engraftment derived from transplanted allogeneic donor progenitor cells compared to recipients treated with PTC.

To test how the transplant of Treg expanded donor cells might affect GVT responses, HSCT experiments were performed using Treg expanded donors and recipients with the B cell lymphoma A20Luc/yfp. Notably, recipients of Treg expanded donor spleen cells exhibited comparable or slightly better GVL activity to that in recipients of non-expanded spleen cells as detected by bioluminescence imaging.

In summary, we developed a novel strategy to rapidly, transiently and markedly expand donor Tregs. Moreover, HSCT performed using Treg-expanded donors compares favorably to HSCT using PTC. Importantly, transplant of Treg expanded donor cells effectively ameliorated GVHD while concomitantly enabling strong anti-tumor responses, supporting the notion that such an approach could provide a promising clinical strategy for the prevention and/or therapy of GVHD.
ARGinine Vasopressin Receptor 1A As a Novel Therapeutic Target for Castration-Resistant Prostate Cancer

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BACKGROUND: Advanced prostate cancer is treated by androgen deprivation but despite initial responses, tumors inevitably recur. The recurrent disease is termed castration resistant prostate cancer (CRPC) and is characterized by androgen receptor (AR) signaling even when circulating androgen levels are minimal. Up-regulation of AR coactivators, such as Vav3, and of constitutively active AR variants, which lack the ligand binding domain, often occur in CRPC and are linked to poor prognosis (1-5). Our lab previously demonstrated that PC cells expressing Vav3 and the prevalent AR variant AR-V7, are growth inhibited by depletion of either Vav3 or AR-V7 (6). To define genes that were dually regulated by AR-V7 and Vav3, we performed gene expression profiling by microarray of the human CRPC cell line 22Rv1 in which Vav3 or AR-V7 were inducibly depleted. We found that arginine vasopressin receptor 1a (AVPR1a), a G-protein-coupled receptor, was significantly reduced by depletion of AR-V7 or Vav3.

DESIGN/METHODS: To explore the role of AVPR1a in PC cells, we selectively depleted AVPR1a in a panel of androgen-dependent and CRPC cell lines as well as in the non-tumorigenic RWPE-1 prostate epithelial cell line and examined cell survival and proliferation in culture and soft agar. To examine whether AVPR1a conferred castration-resistance, we overexpressed it in an androgen-dependent PC cell line LNCaP. Furthermore, to investigate AVPR1a as a drug target, we tested the effects of an AVPR1a-selective antagonist, Relcovaptan, in vitro and in vivo.

RESULTS: We showed that AVPR1a expression was upregulated when AR-V7 and Vav3 were both induced or overexpressed in an in vivo CRPC model. Depletion of AVPR1a greatly inhibited the proliferation of multiple CRPC cell lines but had less marked to no effect on androgen-dependent PC cells or non-tumorigenic prostate epithelial cells. Analysis of cell cycle and apoptosis markers revealed that inhibition of CRPC cell proliferation was due to G1 phase accumulation and/or increased apoptosis. Conversely, overexpression of AVPR1a in androgen dependent LNCaP cells conferred castration resistance in vitro. Further analysis of AVPR1a regulated signaling pathway suggests that it functions through MAPK and may promote AR activity. Similar to depletion of AVPR1a, treatment of PC cells with a selective antagonist, Relcovaptan, resulted in decreased CRPC proliferation in vitro. In a preclinical xenograft model of progression to castration resistance, AVPR1a antagonism halted tumor progression and stabilized prostate specific antigen levels.

CONCLUSION: These results indicate that AVPR1a is a promising new therapeutic target against CRPC. We propose that AVPR1a antagonists may be repurposed for PC therapy.
REBALANCING OF BCL-2 FAMILY PROTEINS MEDIATE THE VULNERABILITY OF PEVONEDISTAT-TREATED ACUTE LYMPHOBLASTIC LEUKEMIA CELLS TOWARDS MEK/ERK PATHWAY INHIBITION

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BACKGROUND: Acute lymphoblastic leukemia (ALL) is the leading cause of cancer-related death in children and the relapse rate in adult ALL patients is about 50%, highlighting the need for new therapeutic strategies. Data from our laboratory and others showed that ALL cells are sensitive to drugs that induce endoplasmic reticulum (ER) stress/unfolded protein response (UPR). In search for novel strategies to target the ER stress/UPR in ALL, we tested the efficacy of the NEDD8-activating enzyme (NAE) inhibitor pevonedistat (MLN4924, pevo) in ALL.

DESIGN/METHODS: We used pharmacological, molecular approaches to target the NEDD8, UPR, and MEK/ERK pathways in ALL cell lines and NSG ALL mouse models.

RESULTS: We found ALL cells exhibited significant in vitro and in vivo sensitivity to pevo-induced ER stress/UPR. Specifically, proteotoxic/ER stress was observed in pevo-treated ALL cells secondary to their inability to halt protein translation following pevo-induced activation of the mTOR pathway and concomitant de-phosphorylation of p-eIF2α (S51). In addition, aberrant activation of MEK/ERK has been correlated with resistance/relapse in pediatric ALL (Blood 2014; 124: 3420-3430). In our Bp- and T-ALL cell line models, we found consistent induction of p-ERK1/2 (T202/Y204) following pevo treatment, suggesting phosphorylation of ERK1/2 as a compensatory survival mechanism in response to pevo’s cytotoxicity. Supporting this hypothesis, we observed significant in vitro synergy between the MEK inhibitor selumetinib (SEL) and pevo (CI = 0.017). On this basis, we tested the in vivo efficacy of pevo + SEL in NSG mice injected with NALM6 cells expressing the luciferase gene (NALM6/LUC). Engrafted NSG mice were treated with pevo (s.c., 66 mg/kg) and SEL (p.o., 50 mg/kg) twice daily on weekdays and once per day on weekends. Bioluminescence analysis of animals 21 days post ALL injection revealed significant reduction of tumor burden in mice treated with pevo alone or pevo + SEL (p<0.05 for both vs. control). Kaplan-Meier curves showed a significant survival advantage for mice treated with pevo + SEL compared with the control group (p<0.05). Mechanistic studies showed that pevo led to induction of NOXA and BIM whereas Mcl-1 levels were stabilized, suggesting sequestration of the pro-survival activity of Mcl-1 by NOXA/BIM. Indeed, co-IP analysis demonstrated that binding between NOXA and/or BIM with Mcl-1 was enhanced in pevo-treated ALL cells. Further, significant downregulation of Mcl-1 was observed in ALL cells co-treated with pevo + SEL. We found that the synergy of this combination was prevented by co-treatment with the pan-caspase inhibitor Z-VAD, but observed persistence of Mcl-1 downregulation whereas BIM expression remained unchanged.

CONCLUSION: Our data indicate that that MEK/ERK pathway inhibition rebalances the Bcl-2 family proteins in favor of synergistic apoptotic death in ALL cells treated in vitro and in vivo with the NAE inhibitor pevonedistat. Our data supports further investigations of agents targeting NAE and the MEK/ERK pathway in relapsed/refractory ALL.
DISCOVERY OF NOVEL INHIBITOR FOR NOTCH ACTIVATION COMPLEX KINASE (NACK)
TARGETING NOTCH PATHWAY IN CANCER

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BACKGROUND: In many human cancers, the Notch signaling pathway has been found to play an important and diverse role in the initiation and maintenance of the neoplastic phenotype. Recently, we have identified and characterized a novel Notch activation complex kinase, NACK, which acts as a Notch transcriptional co-activator and an essential regulator of Notch-mediated tumorigenesis and development. In this regard, NACK could become a putative drug target in anti-cancer therapies.

DESIGN/METHODS: However, NACK (SGK223) is a “dark” kinase, with no bioactivity data and no three-dimensional (3D) protein structure, hindering the development of small molecule inhibitors. To overcome this lack of information, we developed machine learning classification models and performed molecular modeling simulations to elucidate the structural and functional features of NACK and to identify prospective small molecule NACK inhibitors from over 6 million commercially available compounds. Activity of the top compounds was confirmed in colony formation assays, DNA pull down and SPR assays and will be further validated using in vitro and in vivo assays.

RESULTS: The 3D structure of NACK was, for the first time, constructed using Homology Modeling (IntFOLD Server). The optimized 3D structures of ATP bound NACK shed light on the binding interactions at the active site of NACK, which in turn suggest the function of NACK. The hit compounds obtained from Glide Docking, were furthered tested using in vitro and in vivo assays, which showed inhibition of Notch activity.

CONCLUSION: Our approach will open avenues for the development of new therapies for Notch-dependent cancers.
POPULATION-BASED RESEARCH
ASSESSMENT OF SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN DUCTAL CARCINOMA IN SITU (DCIS) DIAGNOSIS IN FLORIDA (1981 – 2013)

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BACKGROUND: In the United States, more than 60,000 women per year with ductal carcinoma in situ (DCIS) are at an increased risk for developing invasive breast cancer. The impact of patient socio-demographic characteristics on outcome variables of women diagnosed with ductal carcinoma in situ (DCIS) diagnosis in Florida has not been explored.

DESIGN/METHODS: A population-based Florida Cancer Data System (FCDS) registry from 1981-2013 was linked with the 2000 US Census data for Floridian women, aged 18 and older, diagnosed with DCIS. Socio-demographic characteristics including race, ethnicity, and neighborhood poverty status (NPS) were assessed against other socio-demographic and clinical characteristics that impact DCIS diagnosis. Descriptive analyses were done to evaluate DCIS burden among these subgroups.

RESULTS: Out of 12,378 patients, the majority of patients were white (87.5%), non-Hispanics (87.7%), between the ages of 50 and 70 years (51.9%), living in middle-high NPS (38%) who were insured privately (39.3%), married (59.7%), and never smoke (50.3%). Black women have similar results except that the majority reside in the lowest NPS (40.2%). Clinical characteristics reveal the majority of women had an unknown (41.3%) or poorly differentiated (25.4%) tumor grade, comedocarcinoma (44%) as histology, a tumor size less than 1.0cm (77%). Majority of women had unknown (48.8%) or positive (41.8%) estrogen receptor (ER) status, unknown progesterone receptor (PR) status (51.2%), and had a form of surgery and radiation as treatment received (79.3%) with the surgery being a lumpectomy/partial mastectomy (61.8%).

CONCLUSION: Assessment of these factors reveal that there are racial disparities in women diagnosed with DCIS. This could be due to blacks being in lower NPS, therefore lacking access to breast cancer screening facilities that allow for cancer detection at the DCIS stage. An analysis of women with invasive breast cancer after DCIS would be needed to confirm this.
UNKNOWN DISPARITIES: ETHNIC HETEROGENEITY AND PROSTATE CANCER MORTALITY IN HISPANIC/LATINO MEN

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BACKGROUND: Few studies have focused on the diverse Hispanic/Latino population in regards to prostate cancer outcomes. Failing to capture ancestral heterogeneity across Hispanic/Latino populations may obscure understanding of disease burden. No other study has attempted to determine whether heterogeneity between Hispanic/Latino men of diverse ancestry contributes to significant variability in prostate cancer-specific mortality relative to non-Hispanic White (NHW) and non-Hispanic Black (NHB) men.

DESIGN/METHODS: We selected for men diagnosed in 2000-2012 with local-regional prostate cancer (n= 432,356) from the Surveillance, Epidemiology, and End Results program, a population-based databank from 18 registries across the country. The compared racial and ethnic groups were: NHW (n= 313,514), NHB (n= 62,346), Hispanic/Latino (n= 36,407), and Asian American/Pacific Islander (n= 20,089). The Hispanic/Latino subgroups were: Mexican (n= 7,273), Puerto Rican (n= 1,174), South or Central American (n= 2,666), Cuban (n= 747), and Dominican (n= 292). The cumulative incidence of prostate cancer-specific mortality (PCSM) for all racial and/or ethnic groups was examined using Fine-Gray competing risks regression. In multivariable analysis, we included age at diagnosis, disease stage summary (localized vs. regional disease), treatment type (none vs. surgery only vs. radiation treatment [RT] only vs. surgery + RT vs. surgery + unknown RT vs. unknown surgery + RT vs. unknown), socioeconomic status composite score, insurance status (uninsured vs. any Medicaid vs. insured vs. unknown), marital status (married vs. others vs. unknown), and residence type (rural vs. urban) for adjustment. In separate univariable and multivariable analyses, NHW and NHB men were used as reference groups.

RESULTS: Compared to NHW men, NHB and Hispanic/Latino men had significantly worse outcomes. In multivariable analysis with NHW men as a reference, NHB (HR= 1.29, 95% CI 1.22 to 1.36, p <0.001) and Hispanic/Latino (HR= 1.12, 95% CI 1.04 to 1.20, p = 0.002) men had significantly worse prostate cancer-specific mortality. In a second multivariable analysis looking at Hispanic/Latino subgroups with the same reference, Puerto Rican (HR= 1.65, 95% CI 1.25 to 2.16, p <0.001) and Mexican (HR= 1.59, 95% CI 1.38 to 1.82, p <0.001) men had significantly higher prostate cancer-specific mortality. With NHB men as a reference, multivariable analysis showed that Mexican (HR= 1.23, 95% CI 1.08 to 1.40, p <0.001) and Puerto Rican (HR= 1.28, 95% CI 0.97 to 1.68, p = 0.084) men had higher prostate cancer-specific mortality, the latter being of borderline significance.

CONCLUSIONS: Our findings suggest that heterogeneity in prostate cancer mortality exists within Hispanic/Latino men and further indicates previously unknown disparities among Puerto Rican and Mexican men. These findings should be considered in screening and management guideline.
ASSESSMENT OF SOCIO-DEMOGRAPHIC CHARACTERISTICS IN STAGE AT PRESENTATION OF CERVICAL CANCER IN FLORIDA (1981–2013): A POPULATION-BASED APPROACH

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BACKGROUND: Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer deaths in females globally. Cervical cancer is now diagnosed at earlier stages due to the implementation of screening programs worldwide, however socio-cultural and financial barriers prevent utilization of such programs. The state of Florida’s diverse population makes it worthwhile to assess disparities in cervical cancer stage at diagnosis.

METHODS: Cervical cancer cases in the population-based Florida Cancer Data System (FCDS) registry from 1981 to 2013 were linked with the 2000 US Census data for adult patients (18 years and older) who are Florida residents. Socio-demographic variables including race, ethnicity, and neighborhood poverty status (NPS) in relation to SEER stage as early (localized) and advanced (regional and distant) stage at presentation were modelled through a multivariate logistic regression model to compare the burden of cervical cancer among these subgroups. Adjusted odds ratio (aOR) and 95% confidence intervals (95%CI) were calculated to determine significant risk factors for being diagnosed in advanced stage cervical cancer. Data management and statistical analysis were performed by SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS: Of 22,676 patients, 78.5% are white and 19.61% are black. Among the patients presenting with late stage cervical cancer at diagnosis, blacks have the highest proportion (58.2%) than other race categories. Similarly, low and middle-low NPS categories combined have the higher proportion (62.2%) than other NPS categories among patients presenting with advanced stage cervical cancer at diagnosis. Further analyses with a multivariate logistic regression model including race, ethnicity and NPS reveals that blacks are more likely to be diagnosed with late stage cervical cancer than whites (aOR=1.37, 95%CI: 1.27 - 1.47). As compared to patients in highest NPS category, there is higher likelihood of diagnoses of cervical cancer at advanced stage in patients in lowest NPS (1.26, 1.14 - 1.39), and in middle-low NPS categories (1.25, 1.14 - 1.36). There is no significant difference between Hispanics and non-Hispanics in cervical stage presentation at diagnosis.

CONCLUSION: Assessment of stage at diagnosis reveals the disproportionate burden of cervical cancer in Blacks compared to other races. Additionally, those of low and middle-low NPS endure the greatest rates of late stage presentation. These analyses indicate a necessity for future evidence-based programs aimed at these more vulnerable groups.
THE PREVALENCE OF HIGH RISK HPV SEROTYPES IN HAITIAN WOMEN WITH CERVICAL CANCER

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BACKGROUND: South Florida has the largest ethnic enclave of Haitian women in the United States. The incidence of cervical cancer in Little Haiti (34 per 100,000 women) is nearly four times higher than that reported for the Miami metropolitan area (9 per 100,000 women). Recent studies have shown that within the Haitian population, the commonest high risk HPV serotypes associated with abnormal cervical cytology were HPV 82, 35 and 61. The prevalence of HPV 16 and 18 in this population was approximately 10%. The primary objective of this pilot study was to describe the high risk HPV serotypes present in cervical cancer specimens of Haitian women. The secondary objective was to determine their impact on survival in this population.

METHODS: A retrospective chart review was performed at Jackson Memorial Hospital, University of Miami Hospital and Sylvester Cancer Center of 40 Haitian patients diagnosed with invasive cervical cancer between 2007-2013. Data collected included: age, race, body mass index, mode of treatment, recurrence status, tumor stage, grade and histology. Cervical carcinoma tissue samples were obtained from these patients at the time of diagnosis. DNA was extracted with the QIAamp DNA FFPE Tissue Kit following xylene-ethanol deparaffinization. Cervical samples were tested for HPV types 16, 18, 31, 33, 35, 45, 52, 53, 66, 68, and 82 using multiplex PCR with type-specific primers. β-globin was used as a positive control. HPV type was determined using gel electrophoresis. Survival analyses were performed with the Kaplan-Meier method and compared using log-rank testing.

RESULTS: 34 (85%) patients had successful extraction of DNA from cervical cancer tissue specimens and 6(15%) had a failed extraction and were therefore excluded from the analysis. The commonest high risk HPV serotype found was HPV 16 (85.3%). This was followed by HPV 31 (11.8%), HPV 18 (8.8%), HPV 35 (5.9%) and HPV 66 (5.9%). The co-infection rate seen in this cohort was 23.5% (N=8). There was no difference in overall survival between those patients with co-infection versus single infection, P=0.13.

CONCLUSION: HPV 16 is the most prevalent serotype found in cervical cancer of Haitian women. There is a higher than expected coinfection rate. Larger studies are needed to further explore the significance of these co-infections and may direct future preventive and screening strategies in this population.
NON-HOMOLOGOUS END JOINING PATHWAY ASSOCIATED WITH PAIN AMONG BREAST CANCER PATIENTS RECEIVING ADJUVANT RADIATION THERAPY: GENE SET ANALYSIS

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BACKGROUND: Pain related to cancer or treatments is a critical quality of life (QOL) issue for breast cancer survivors. This study aimed to evaluate the association between polymorphisms in DNA damage/repair pathways and radiation therapy (RT)–associated pain among breast cancer patients receiving adjuvant RT.

METHODS: Pain score was assessed at pre- and post-RT as the mean of four pain severity items (i.e., pain at its worst, least, average, and now) from the Brief Pain Inventory with 11-point numeric rating scale (0-10) and RT-associated clinically relevant pain was considered present when pain score increased from <4 to ≥ 4 during RT. We included 8 DNA damage/repair pathways using the PLINK set-based test: base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), homologous recombination, non-homologous end-joining (NHEJ), RNA polymerase, cell cycle, and p53 signaling pathway.

RESULTS: 359 patients were included in this study and 81 developed RT-associated pain (22.6%). The NHEJ pathway was associated with RT-associated pain (p=0.0399). This associated was mainly driven by genetic variations in XRCC5 (p=0.045), XRCC4 (p=0.059), and XRCC6 (p=0.074). We examined the most significant and independent SNPs in each gene separately to determine which SNPs are driving these significant associations. Most significant association was found in XRCC4 (rs2089565) variant which showed that carrying at least one minor C allele was associated with increased risk of RT-associated pain (odds ratio [OR]=1.90; 95% confidence interval (CI)=1.30-2.78, p=0.0009). For XRCC5 variant (rs1364726), carriers with at least one minor T allele were less likely to develop RT-associated pain (OR=0.39; 95% CI=0.20-0.77, p=0.007).

CONCLUSION: This study demonstrated that genetic variations in multiple genes in NHEJ pathway may contribute to inter-individual variation in pain experience among cancer patients during RT. After validation with a larger sample, these findings may be used as predictive biomarkers of radiation sensitivity which allows to identify patients at high risk of pain. Also the results can provide biological targets for early intervention for pain management to improve QOL in breast cancer survivors.

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EFFECTS OF STRESS ON THE SYMPATHETIC NERVOUS SYSTEM ACTIVITIES OF FAMILY CAREGIVERS OF ADULT CANCER PATIENTS

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BACKGROUND: Cumulative evidence shows cancer caregivers are at greater risk for premature morbidity compared to non-caregivers. Recent evidence implies their poor physical health may be attributable to their elevated stress from caregiving. The extent to which caregiving experiences relate to sympathetic nervous system (SNS) activities, physiological markers of health, among cancer caregivers is yet unknown.

METHODS: Family caregivers of colorectal cancer patients (N=91; age M=47 years; 75% female; 64% Hispanic; time since patient diagnosis M= 3.5 months) participated in the study. Primary outcomes were cortisol, dehydroepiandrosterone-sulfate (DHEAS), and alpha-Amylase (AA), assayed from the saliva sample as non-invasive assessment of SNS activities. Primary predictors were caregivers’ self-reported perceived stress from cancer (Cancer Appraisal Scale), caregiving (Pearlin Stress Scale), and family obligation (Familism). Covariates were age and gender.

RESULTS: Results of multivariate general linear modeling showed that at awakening, greater perceived stress from cancer related to higher AA (B=47.47, p<.01), and greater family obligation marginally related to lower AA and DHEA-S (B=-34.82, -0.42, ps<.08, respectively). At bedtime, greater perceived stress from cancer was again related to higher AA (B=44.50, p<.05); and family obligation was marginally related to higher DHEA-S and lower cortisol (B=0.78, -5.42, p<.07, respectively).

CONCLUSION: Findings suggest perceived stress from having cancer in the family has a substantial impact on the family caregivers’ SNS activity levels around the time of diagnosis, which potentially have long-term health implications if not managed properly. Future investigation on diverse sources of cancer-related stress and long-term health consequences of such stressor is warranted.
THE ROLE OF ETHNICITY IN STRESS RELATING TO ALPHA AMYLASE IN FAMILY CANCER CAREGIVERS.

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BACKGROUND Cancer imposes stressful challenges to the family caregivers that are likely to be exacerbated by existing chronic stress and alleviated by existing resources. Those individual-level sociocultural risk and resource factors are also likely to play different roles by ethnic groups. We tested, with family caregivers of colorectal cancer patients, (a) the effects of stress from perceptions of discrimination and social support (chronic factors) and of becoming a caregiver (acute factor) on alpha-amylase (AA), a stress biomarker; and (b) the role of ethnicity in these associations.

DESIGN/ METHODS Family caregivers of cancer patients who were newly diagnosed with colorectal cancer participated in the study (N =92, 50 years old; 75% female; 64% Hispanic; 3-mn post-diagnosis). Caregivers collected saliva at wake-up and bedtime for two consecutive days; AA was assayed and served as an outcome. Perceived discrimination (Perceived Discrimination Scale), caregiving stress (Pearlin Stress Scale), social support (ISEL), and ethnicity (Non-Hispanic White vs Hispanic) were primary predictors. Age was a covariate.

RESULTS Caregivers were comparable between the two ethnic groups in study variables, except that Hispanics reported lower levels of perceived discrimination, unexpectedly, than Whites (p<.04). Hierarchical regression analyses revealed that awakening AA was positively related to older age (β=.37, p<.001). Bedtime AA remained related to older age, but more weakly (β=.22, p<.04). Above and beyond age, greater perceived discrimination related to higher bedtime AA among Hispanics (β=.18) but lower bedtime AA among non-Hispanic Whites (β=-.31), p<.04. Caregiving stress and social support were not related to AA, regardless of ethnicity.

CONCLUSIONS Findings suggest that chronic stress, such as discrimination, is manifested differently in biomarkers between Hispanics and non-Hispanic Whites during the time after the cancer diagnosis of a family member. Testing the assumption of the Reserve Capacity Model, investigation of long-term health outcomes of Hispanic caregivers’ perceived discrimination is warranted. Unexpected findings of White caregivers reporting greater discrimination and its relation to better biological regulation at bedtime need to be replicated for meaningful interpretation. Longitudinal investigation including other ethnic groups and sociocultural risk and resource factors will be fruitful.
EFFECTS OF A POSITIVE AND NEGATIVE OUTLOOK ON THE PHYSICAL HEALTH OF CANCER PATIENTS AND THEIR CAREGIVERS

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BACKGROUND: Cancer diagnosis is an unexpected stressful event not only to patients but also to their family caregivers. Studies suggest that outlooks, such as optimism and uncertainty, play a significant role in one’s psychological adjustment to a life-changing event. Unknown, is whether these outlooks would relate similarly to physical health. Moreover, unknown is the extent to which caregivers’ own outlook relates to their patients’ physical health, and vice versa. The purpose of this study was to examine the role of individuals’ general outlook, such as optimism and uncertainty, in the physical health of colorectal cancer patients and their caregivers.

DESIGN/METHODS: Patients who were newly diagnosed with colorectal cancer and their family caregivers participated. A total of 54 patient-caregiver dyads’ data were subject to analysis (N=108, 3-month post-diagnosis, mean age 53 and 49, 76% and 80% Hispanic, for patients and caregivers respectively). Optimism (LOT-R), uncertainty (Mishel’s Uncertainty in Illness), and physical health (MOS SF-12) were self-reported. In addition, participants collected saliva samples 3 times per day for 2 consecutive days, from which cortisol slope was calculated. Cancer stage served as a covariate.

RESULTS: Both patients and caregivers reported moderate levels of optimism and uncertainty about the cancer prognosis. Actor-Partner Interdependence Modeling revealed that patients’ optimism positively related to their own steeper decrease in cortisol slope from awakening to bedtime (β=-.27, p<.04) and their caregivers’ better physical health (β=.23, p<.05). On the other hand, caregivers’ optimism positively related to their own better physical health only (β=-.31, p<.01). Caregivers’ uncertainty related to their own poorer physical health (β=-.26, p<.03).

CONCLUSION: The results highlight the significant roles of optimism and uncertainty in physical health. Furthermore, findings suggest patients’ positive outlook has a spill-over effect on their caregivers’ physical health during the time of cancer diagnosis. Current findings need to be replicated with a longitudinal investigation with a larger sample and diverse biological health indicators. Identifying psychosocial and biobehavioral mechanisms of the link of optimism and uncertain to one’s own and the other family member’s physical health is warranted in future studies.
UNRESECTABLE HEPATOCELLULAR CARCINOMA: IS RADIO- EMBOLIZATION AN ALTERNATIVE FOR CHEMOEMBOLIZATION?

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Running title: Therapeutic Embolization of Unresectable Hepatocellular Carcinoma

BACKGROUND: Transarterial Radio-embolization (TARE) has emerged as a newer regional technique to Transarterial Chemo-embolization (TACE) for treatment of unresectable hepatocellular carcinoma (HCC). The aim of this study is to evaluate clinical outcomes of both techniques.

DESIGN/METHODS: Online search for studies comparing TARE to TACE from 2005 to present was performed. Primary outcome was overall survival rate for up to 4 years. Secondary outcomes included post-treatment complications and treatment response. Quality of included studies was evaluated by STROBE criteria. Relative Risk (RR) and 95% Confidence Intervals (CI) were calculated from pooled data.

RESULTS: The search strategy yielded 172 studies, 5 met our selection criteria and included 653 patients undergoing embolization for unresectable HCC. Of these patients, 284 underwent TACE and 269 underwent TARE. Median age was 63 and 64 years for TACE and TARE, respectively. Meta-analysis showed no statistically significant difference in survival for up to 4 years between the two groups (HR=1.06; 95% CI: 0.81-1.46, p=0.567). TACE required at least one day of hospital stay compared to TARE which was mostly an outpatient procedure. TACE had more post-treatment pain than TARE (RR=1.96, 95% CI: 1.40-2.75, p<0.01), but less subjective fatigue (RR=0.62, 95% CI: 0.48-0.80, p<0.01). There was no difference between the two groups in the incidence of post-treatment nausea, vomiting, fever or other complications. In addition, there was no difference in partial or complete response rates between the two groups.

CONCLUSION: TARE appears to be a safe alternative treatment to TACE with similar complication profile and survival rates. Larger prospective randomized trials, focusing on patient-reported quality-of-life are required to consolidate these results, and to evaluate cost vs benefit for both techniques.
Socio-Demographic Disparities in the Stage at Diagnosis of Kaposi Sarcoma in Florida Before and After the Introduction of Highly Active Anti-Retroviral Therapy: A Population Based Study (1981-2013)

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Background: Kaposi Sarcoma (KS) is the most common cancer among HIV patients in the US and the State of Florida leads the nation in reporting new HIV cases. Introduction of highly active antiretroviral therapy (HAART) in 1996 has been associated with marked decline in the incidence and prevalence of KS. However, disparities based on the access to and utilization of that treatment may exist.

Design/Methods: The Florida Cancer Data System (FCDS) Registry (1981-2013) is linked with the 2000 US Census to obtain data on adult Floridians (age 18-70 years), who were diagnosed with KS. Neither FCDS nor US Census data included any information about patients' HIV status at the time of diagnosis. Disparities in socio-demographic factors (age, gender, race/ethnicity, neighborhood poverty status (NPS), health insurance, smoking status) relative to the KS stage at diagnosis as early (localized) and advanced (regional and distant) were modelled using multivariate logistic regression models by pre-HAART (before 1996) and post-HAART (1996 and after) era. Adjusted odds ratio (aOR) and 95% confidence intervals (95% CI) were calculated to determine significant risk factors for being diagnosed in advanced stage KS. Data management and statistical analysis were performed by SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results: Out of 3,226 patients, the majority were males (93.2%), white (77.5%), non-Hispanic (73.7%), with low/middle-low NPS (68.3%), and diagnosed in pre-HAART era (65.7%). Overall, the proportion of advanced-stage KS declined from 81.6% in pre-HAART era to 39.9% in post-HAART era. Younger patients (age 18–50 years) were more likely to be diagnosed with advanced stage KS than older patients (age 51–70 years) both in pre-HAART (aOR=2.34, 95% CI: 1.68 – 3.28) as well as in post-HAART era (1.62, 1.15 – 2.28). The proportion of whites in post-HAART era decreased from 88.7% to 69.5% and from 81.2% to 64.9% in early and advanced stages, respectively. However, the proportion of blacks increased from 11.3% to 29.3% and from 18.7% to 33.1%, in early and advanced stages, respectively. As compared to whites, blacks were found to have more likelihood of getting diagnosed with the advanced stage KS, both in pre-HAART (1.66, 1.13 – 2.44) as well as in post-HAART era (1.56, 1.14 – 2.14). The higher likelihood of advanced stage KS at diagnosis for Hispanics, as compared to non-Hispanics, changed from non-significant in pre-HAART (1.29, 0.98 – 1.69) to significant in post-HAART era (1.47, 1.08 – 2.00). The relationship of NPS with KS stage at diagnosis was borderline significant only when lowest NPS was compared with highest NPS in pre-HAART era (1.51, 1.01 – 2.24). Otherwise, the relationship was found to be non-significant when all NPS levels were compared with highest NPS category, both in pre-HAART and post-HAART era.

Conclusion: Trends reveal more diagnosis of KS at early stage in the post-HAART era. Along with an increasing proportion of blacks diagnosed with KS in both stages in both the eras', there is a persistent high likelihood of blacks having advanced stage KS at diagnosis in both eras. Contrary to pre-HAART era, Hispanics developed higher likelihood of advanced stage KS at diagnosis as compared to non-Hispanics in post HAART era. Introduction of the treatment is discordantly affecting race and ethnicity, favoring whites and non-Hispanics, resulting in an increase in racial/ethnic disparities in the post-HAART era. Our study results highlight the importance of introducing promising interventions to eliminate emerging disparities.
SHARED RESOURCES
NON-COMPETITIVE
ANALYTICAL IMAGING CORE FACILITY
Core Manager: Marcia Boulina, Ph.D.
http://sylvester.org/shared-resources/analytical-imaging

DESCRIPTION/PURPOSE: The Analytical Imaging Core Facility at Sylvester supports the development and use of novel imaging and analytical approaches to advance scientific research. It provides researchers with access to costly state-of-the-art analytical and imaging techniques for cellular and tissue imaging as well as molecular analysis of pathology specimens. The core also trains investigators, fellows, and technical staff in the proper use of these sophisticated techniques and instruments.

EQUIPMENT/TECHNOLOGIES:
- Leica SP5 inverted confocal microscope with motorized stage, tile scanning, fast galvo-Z focusing, high resolution and fast resonance scanners. New HyD detectors.
- Leica MP-NDD4/SP5/FCS/FLIM multiphoton/confocal microscope with 4 non-descanned detectors, 5 PMTs, saline "dipping" objective lenses
- Zeiss ApoTome Axiovert 200M + Zeiss Axiovert 200M/ORCA-ER MetaMorph microscope
- Leica AS LMD laser microdissection
- Leica DMIRB Inverted Microscope with Leica DFC495 color camera for histology and immunohistochemistry
- MetaMorph Imaging System
- Pathscan4 histology/immunohistochemistry microscope slide scanner, Epson V750-M flatbed scanner

SERVICES:
- Leica Confocal Microscopy (9 laser lines, 5 channel fluorescence, tile scanning)
- Leica Multiphoton/Confocal Microscopy (Coherent Chameleon Ultra II multi photon laser, 9 confocal laser lines, 3 imaging PMTs), saline "dipping" lenses
- High Content Screening (including timelapse, physiology, Fura-2 ratio imaging, optional confocal)
- Fluorescence Microscopy (widefield, deconvolution and ApoTome digital optical sectioning)
- Laser Microdissection
- General Microscopy (widefield fluorescence, phase contrast, light microscopy)
  - Two fluorescence microscopes: Zeiss Axiovert 200M microscopes; ORCA scientific grade monochrome cameras
  - One histology/immunohistochemistry brightfield microscope: Leica DMIRB with Leica DFC495 color camera
- Image Analysis
- Pathscan4 microscope slide scanning (3.6 um pixel size) and Epson V750-M flatbed scanning
- Also available:
  - Training, consultation, and direct assistance to investigators and graduate students
  - Seminars to update researchers on core services

SERVICE CHARGES:
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CONTACT: Marcia Boulina, Ph.D., Core Manager
305-243-8436, mboulina@med.miami.edu

LOCATION: Diabetes Research Institute
1450 NW 10th Avenue,
6th Floor (Room 6025)

SCHEDULING: Web-based scheduling system: http://sccc.ccs.miami.edu/AICFScheduler
**BIOSTATISTICS AND BIOINFORMATICS CORE (BBC)**

Core Director: Xi (Steven) Chen, Ph.D.


**DESCRIPTION/PURPOSE:** Provide the investigators at UM Sylvester with cutting edge, state of the art biostatistical, bioinformatics, and computational expertise for cancer research. Members of the BBC contribute to all phases of research, including statistical study design, data analysis, interpretation of quantitative findings, and comprehensive high throughput genomic data analysis. The Core is also actively involved in teaching and training of investigators, fellows and research staff in the use of cutting edge software systems and analysis methods.

**SERVICES:**

**BIOSTATISTICS**
- Design of clinical and population studies and laboratory experiments
  - Study design and sample size determination/justification
  - Statistical analysis plan for interim and final results
  - Early stopping guidelines for data and safety monitoring
- Write-up of statistical considerations for grants and protocols
- Data analysis and interpretation of findings throughout the project
  - Write-up of statistical methods and results for manuscripts, abstracts, presentations, and reports to oversight committees and funding agencies
  - Consultation for database design and data management
  - Assistance with protocol amendments

**BIOINFORMATICS**
- Experiment design for high-throughput genomic studies
- Next-Generation Sequencing Data Analysis including RNA-Seq, ChIP-Seq, Exome/Whole Genome Sequencing and other NGS technologies
- Pathway/Gene Set Enrichment Analysis and Gene Network analysis
- Genomic data integration using public database such as TCGA and GEO
- Bioinformatics new methodology and algorithm development
- Bioinformatics software development including Bioconductor/R package and web-based software

**SERVICE CHARGES:**
- Pre-award work: Collaborative support in the development of research grant proposals, letter of intents (LOI), clinical trial protocols are usually fully or partially supported by the SCCC at no charge provided that the corresponding study budget will include % effort for BBC members involved in the project.
- Post-Award: Cover by grant % effort support for BBC members.
- Other services: Collaboration agreement or hourly charge.

**CONTACT:**
Lola Sumner, MA, Sr. Manager, Business Operations
305-243-2865 / 305-243-3957
bbc@med.miami.edu / lsumner@med.miami.edu

**LOCATION:**
Clinical Research Building, 10th Floor, Room 1050
DESCRIPTION/PURPOSE: The Disparities and Community Outreach Core’s (DCO) mission is to support community-engaged research that addresses the unique needs of our diverse catchment area, including disparities in cancer incidence, morbidity, and mortality at the University of Miami Sylvester Comprehensive Cancer Center. The core provides consultation on study design and delivery for community engaged research initiatives, facilitates access to Jay Weiss Institute’s network of community partners for research collaboration and effective translation of new discovery, and offers timely, high quality services to support community-engaged research in South Florida.

The core offers pre-and-post award services to investigators including consultation on research design and study implementation, development of community research partnerships, as well as project coordination and management; protocol development and regulatory management. The Core also promotes Community-Based Participatory Research (CBPR) methodologies and engages community representatives who provide direction to investigators on outreach, recruitment, implementation and dissemination.

SERVICES:
• Pre-Award Services (no charge to Sylvester investigators)
  o Community profiles: provide supporting information for grant proposals including cancer surveillance and socio-demographic data and narrative descriptions of communities or populations.
  o Community Support: connect investigators to input and letters of support from Community Advisory Board members and Community Leadership Board.
  o Research partnerships: establish and negotiate research partnerships with community-based organizations.
  o Culturally and linguistic Design: consult on appropriate study design, recruitment and retention strategies, study materials, and participant incentives.
• Post-Award (Fee-Based) Services
  o Community Engagement: facilitate academic-community partnerships to aid in the recruitment of subjects, retention and dissemination of findings, MOUs and promotion within communities.
  o Participant Recruitment: screen on EHR, provide informed consent process, conduct follow up with study participants
  o Protocol Development and Regulatory Management: aid in the IRB process and compliance with federal, state and university regulatory requirements
  o Data & Specimen Collection: conduct qualitative and quantitative data collection, plan and facilitate focus groups, and assist in bio specimen collection
  o Study Materials Development: design and adapt recruitment flyers, consent forms, survey instruments, and focus group questions that are culturally, linguistically, and literacy-level appropriate for the study population.
  o REDCap Database, Data Entry, Management: offer database development and training, and database maintenance throughout the project
  o Translations and Transcription: provide IRB ready translations of documents used in research (such as informed consent forms and questionnaires) from English to Spanish and Creole
  o Training and Education: conduct tailored CBPR, cancer health disparities, cultural competency and CHW training.

SERVICE CHARGES: Please call for current rates

CONTACTS: Erin Kobetz, Ph.D., Core Director
305-243-6185, ekobetz@med.miami.edu
Martine Poitevien, MBA, CCRP
305-243-4630, Mpoitevien@med.miami.edu

LOCATION: Clinical Research Building, Room 1004
1120 NW 14th Street, Mail Stop R-669

CONSULTATION: Get started with the DCO Core: https://redcap.med.miami.edu/surveys/?s=XmaJB3hykm
LIVE TUMOR CULTURE CORE (LTCC): CELL LINES IN THE BUSINESS OF REVEALING CANCER SECRETS

A. Sousa, M. Jones and T. Ince

Department of Pathology, Sylvester Comprehensive Cancer Center, Braman Family Breast Cancer Institute and Interdisciplinary Stem Cell Institute, University of Miami Miller School of Medicine

BACKGROUND: The Analytical Imaging Core Facility at Sylvester supports the development and use of novel imaging and analytical approaches to advance scientific research. It provides researchers with access to costly state-of-the-art analytical and imaging techniques for cellular and tissue imaging as well as molecular analysis of pathology specimens. The core also trains investigators, fellows, and technical staff in the proper use of these sophisticated techniques and instruments.

DESIGN/METHODS: We have developed a new cell culture system to routinely establish cell lines that retain the accurate differentiation phenotype and molecular profile of the original tumor.

RESULTS: Our lines are authenticated by STR profiling (compared with original tumor), validated by malignancy and biomarker assays and annotated with clinical information and follow up of patient outcome. Here we introduce the Live Tumor Culture Core (LTCC) where viable tumor tissues are collected in collaboration with the Tissue Bank Core Facility (TBCF) and used by our team to establish large panels of much needed new cancer cell lines that recapitulate the original tumor.
NON-THERAPEUTIC RESEARCH SUPPORT CORE
Core Director: Suzanne Lechner, Ph.D.

http://sylvester.org/shared-resources/non-therapeutic-research-support-core

DESCRIPTION/PURPOSE: The Non-Therapeutic Research Support (NRS) Core provides direct research support services to investigators conducting all types of non-therapeutic research at the Cancer Center (such as biobehavioral, epidemiologic, bench science, observational clinical trials).

Non-therapeutic cancer studies may include prevention, control, survivorship and other non-drug/device oncology-related studies. The NRS Core provides expert guidance on research design, study development, and study initiation. Investigators access a wide range of research support services for tasks conducted in Sylvester, Jackson, and Medical campus clinics (including Sylvester satellite clinics), including: IRB protocol development, eligibility screening, informed consent, data collection, general study coordination tasks, research trial interventionist services, administering questionnaires, biospecimen collection and shipment, and staff education and training in non-drug/device trials.

Research services are provided by highly skilled Master’s level coordinators and project managers who are supervised by a Ph.D.-level scientist with over 15 years of experience in conducting human subjects research.

SERVICES:
1. Provide direct research support services for non-therapeutic research on a fee-for-service basis
2. Training in the appropriate conduct of non-therapeutic trials
3. Serve as liaison between investigators and existing resources and University-wide research units
4. Provide expert guidance on the design and implementation of non-therapeutic trials

TECHNOLOGIES:
- **Research Activity software (commercial):** Qualtrics, REDCap data collection, Internet Survey packages, MS Office, Adobe Acrobat suite, MS Sharepoint
- **Database software:** MS Access and REDCap (http://project-redcap.org/)

CONTACTS: Madeline Krause, M.S.Ed., Core Manager
305-243-3329
Madeline@miami.edu

Suzanne Lechner, Ph.D., Scientific Director
SLechner@med.miami.edu

LOCATION: Clinical Research Building, Room 1481a
1120 NW 14th Street, C-202

SCHEDULING: Advance notice is required.
ONCOGENOMICS CORE FACILITY
Core Director: Sion Williams, Ph.D.

http://sylvester.org/shared-resources/oncogenomics

DESCRIPTION/PURPOSE: The Oncogenomics Core Facility (OCF) is a state-of-the-art open-core facility created in 2007 and located in the in the Biomedical Research Building (BRB). The OCF provides investigators access to a wide range of services for the study of functional genomics with a strong focus on applications for epigenetics. The facility employs four full-time Research Associates and a faculty-level Director overseen by a Shared Resources and Cancer Epigenetics Program leadership. Services span RNA/DNA extraction and QC, qPCR, droplet digital-PCR, PCR-free gene expression assays, single-cell sample prep and gene expression analysis, miRNA and CNV assays, and rapid run next generation sequencing.

EQUIPMENT/TECHNOLOGIES:
• Illumina NextSeq 500 sequencer
• NanoString MAX system
• Fluidigm C1 single cell autoprep system
• Fluidigm Biomark HD nanofluidic qPCR system
• Raindance Raindrop droplet digital PCR system
• Bio-Rad QX200 droplet digital PCR system
• Two Roche Lightcycler LC480 qPCR machines with autoloader & refrigerated plate stacker
• Agilent Bioanalyzer 2100, nanoDrop n8000, and Qubit 3.0
• Eppendorf epMotion 5075 automated pipetting system
• Bio-Rad C1000 deep well PCR machine
• Eppendorf MasterCycler Pro-S PCR machine
• Thermo Fisher swing bucket centrifuge
• Covaris Cryoprep

SERVICES:
1) Nucleic Acid Extraction, quantification & QC: Extraction, quantification and QC of DNA/RNA from all sources including cells, tissue, biofluids, FFPE and low input specimens.
2) Gene Expression & Molecular Counting Assays: This category comprises assays quantify RNA or DNA targets without generating sequence data. The most common application is for examining gene expression including miRNA assays. These approaches can also be used to look at viral load and copy number variation. Services falling into this category include NanoString, ddPCR, qPCR.
3) Next Generation Sequencing: The OCF acquired an Illumina NextSeq 500 in 2014 to support the focus on epigenetics services. A broad range of services can be run using this technology. Principle services are the library prep and sequencing components of RNA-Seq methodologies including whole transcriptome, GRO-Seq, Ribo-Seq etc. Sub-genomic DNA-Seq approaches are also covered such as ChIP-Seq, ATAC-Seq and amplicon sequencing.

Contact core directly or visit web-site or iLab portal for a full list of services and fees

CONTACT: Sion Williams, Ph.D., Core Director
305-243-3875, SLWilliams@miami.edu

iLAB: https://umiami.corefacilities.org/service_center/3405/?tab=services

LOCATION: Biomedical Research Building (BRB) 542c, 1501 NW 10th Avenue
**SIMULATION-BASED ESTIMATION OF MEAN AND STANDARD DEVIATION FOR META-ANALYSIS USING APPROXIMATE BAYESIAN COMPUTATION (ABC) COUPLED WITH MODEL AVERAGING METHOD.**

Deukwoo Kwon and Isildinha M. Reis

ENAR

When conducting a meta-analysis of a continuous outcome, estimated means and standard deviations from the selected studies are required in order to obtain an overall estimate of the mean effect and its confidence interval. If these quantities are not directly reported in the publications, they must be estimated from other reported summary statistics, such as the median, the minimum, the maximum, and quartiles. In our previous publication, we proposed a simulation-based estimation approach using the Approximate Bayesian Computation (ABC) technique for estimating mean and standard deviation based on various sets of summary statistics found in published studies. Our approach outperformed the other available methods when data are generated from skewed or heavy-tailed distributions and provided similar results under symmetric distributions.

The previous ABC with single distribution selection (ABC-SD) was based on assumed single parametric distribution of original data. In most situations, we need to choose one distribution from several candidate distributions, using posterior model probability. We found that the selection of an underlying distribution via posterior model probability was sensitive to the chosen prior distribution for parameters.

In this study, we exploit the use of ABC with Bayesian model averaging methodology (ABC-BMA) to estimate mean and standard deviation. We show that ABC coupled with model averaging of several candidate distributions performs better than the previous ABC with single distribution selection in terms of the average relative errors (AREs).
Integration of genes into the mouse genome can serve as an experimental system to study normal as well as altered gene expression. Such studies can also serve to identify genes essential for normal development and generate animal models for human diseases. The Transgenic Animal Core Facility at Sylvester uses powerful transgenic/gene knockout/gene knock-in technologies to study the function of genes in vivo. The core produces low-cost transgenic and gene targeted-mutant mouse models. It provides gene engineered mouse model design, ES cell manipulation, DNA and ES cell injection service to all UM as well as external investigators. The facility also provides service on mouse strain rederivation, embryo cryopreservation and IVF procedures for frozen sperm. The purpose of the Transgenic Animal Core Facility is to provide a centralized service to efficiently produce transgenic and gene targeting mouse models for basic research. This should result in reduction in effort and cost to UM as well as external investigators. This core consists of 3 parts that includes a basic research lab, an animal facility and several injection rooms. The basic lab is doing the gene targeting vector construction, ES cell manipulation and all of the molecular cellular biological work. The animal room provides housing and breeding space for the mice involved in the transgenic and gene targeting projects. The injection rooms are fully equipped to carry out the entire procedure of making transgenic mice.
TUMOR BANK CORE FACILITY
Core Directors: Tan Ince, M.D., Ph.D. & Carmen Gomez-Fernandez, M.D.
http://sylvester.org/shared-resources/tissue-banking

DESCRIPTION/PURPOSE: The Tumor Bank Core Facility (TBCF), which holds a NIH certificate of confidentiality, is designed to bank tissue and paired clinical data for UM investigators who have an IRB approved project. The TBCF employs a tumor bank manager who oversees daily activities, compliance, regulations and scheduling. The manager provides an interface with the investigators to coordinate data and tissue acquisition, tissue inventory, data entry, and general maintenance of the facility. The manager is assisted by support staff, including two pathology assistants that are responsible for tissue acquisition and frozen section analysis following resection and are responsible for consenting patients. There is also a fulltime pathologist on staff with the bank.

EQUIPMENT/TECHNOLOGIES:
- (4) -80°C freezers; LN2 storage; -20°C & 4°C storage; tissue culture hood; Galileo TMA CK 3500 Processor; microscopes
- Computer software (CaTissue/Brady)
- Hardware and barcoding instrumentation (Brady Printer, Code Scanner)

SERVICES: UM investigators who wish to utilize tumor or normal control tissue and data from the bank are asked to provide 1) an IRB approval letter for the project (or an IRB Exemption Letter) and 2) a proposal for the use of tissues to be reviewed by the appropriate site disease group. Once the request is submitted and approved, the investigator is asked for a Standard Operating Procedures (SOP) detailing the exact requirements for procurement of their specimens. The investigators are invoiced monthly for the collection of their specimens. The de-identified tissue samples and the appropriate clinical history are distributed as requested by the investigator.

Collecting for your study-recruitment: For those investigators who are interested in having us collect fresh tissue and blood for your IRB-approved study, or surgeons who would like to contribute to the bank, please contact the Tumor Bank.

Consenting: We are equipped and approved to consent in clinic, pre-op, and post-operatively (special circumstances). We prefer to consent them on the day of surgery in pre-op, but in special circumstances we can consent post-operatively.
   In the clinic: When patient is appropriate for collection please notify the Tumor Bank as early as possible.
   Pre-Op: We review surgical schedules daily for collection, but also ask the PI, nurse, coordinator or admin. assistant for your study to let us know LOCATION, TIME, PATIENT NAME, AND MRN as much in advance as possible via email which allows us to coordinate consenting with collection. Please note that all tissue collected through the bank will be available to all UM investigators (in consultation with the PI of specific collections).

Tissue Microarray (TMA) Preparation: The Tumor Bank has the facilities to prepare custom made TMAs. These can be made from archived or prospectively collected tissue; or from an investigator’s archived blocks of human or animal tissue. The cost of this service is currently under review.

CURRENT SERVICE CHARGES: Subject to change

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<td>Consenting</td>
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<td>PA Tissue Procurement</td>
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<td>Paraffin Block Recovery</td>
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CONTACT: 305-243-6777, TBCF@med.miami.edu
LOCATION: Fox Building 436
1550 NW 10th Avenue

SCHEDULING: Advance notice is required