Spring 2017 Cancer Research Conference

UAMS + UTHSC in Partnership with West Cancer Center

May 2, 2017 | Memphis, TN

UAMS
University of Arkansas for Medical Sciences

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

The University of Tennessee WEST Cancer Center
Methodist Healthcare Family

Program Outline
Morning Session

10:00am-10:20am	**Arrival - Continental Breakfast**
10:20am-10:30am	**Welcome** Dr. Steven R. Goodman, Vice Chancellor for Research at UTHSC and Dr. Larry Cornett, Vice Chancellor for Research at UAMS
10:30am-10:50am	**"Clinical Advances in Hormone Receptor Positive Breast Cancer"** Dr. Lee Schwartzberg The University of Tennessee Health Science Center
10:50am-11:10am	**"Overview of Cancer Research at the Winthrop P. Rockefeller Cancer Institute"** Dr. Peter Emanuel The University of Arkansas for Medical Sciences
11:10am-11:30am	**"Comorbidity Factors Associated with Human Papillomavirus Infectivity: Implications in Cervical Cancer Health Disparity"** Dr. Subhash C. Chauhan The University of Tennessee Health Science Center
11:30am-11:50am	**"Translational Drug Development: Research that Takes you From Bench to Bedside and Beyond"** Dr. Hong-yu Li The University of Arkansas for Medical Sciences
11:50am-12:00pm	**Question & Answer Session for Talks #1-4**
12:00pm-1:30pm	**Poster Presentations and Lunch**

Program Outline
Afternoon Session

1:30pm-1:50pm	**"Targeting Senescent Cells to Improve Cancer Therapy"** Dr. Daohong Zhou The University of Arkansas for Medical Sciences
1:50pm-2:10pm	**"Highlights of Women's Basic/Pre-clinical Cancer Research at UTHSC: Opportunities for Collaboration"** Dr. Tiffany Seagroves The University of Tennessee Health Science Center
2:10pm-2:30pm	**"Cancer Prevention and Population Sciences Program at the UAMS Winthrop P. Rockefeller Cancer Institute"** Dr. L. Joseph Su The University of Arkansas for Medical Sciences
2:30pm-2:50pm	**"HPV, Epigenomics and Anal Cancer"** Dr. David Shibata The University of Tennessee Health Science Center
2:50pm-3:00pm	**Question & Answer Session for Talks #5-8**
3:00pm-3:10pm	**Closing Remarks** Dr. Steven R. Goodman, Vice Chancellor for Research at UTHSC and Dr. Larry Cornett, Vice Chancellor for Research at UAMS
3:10pm-3:30pm	**Informal Gathering-Afternoon Snack**

UTHSC/UAMS CORNET Awards
Collaborative Research Network
in Cancer Research

Purpose: To stimulate innovative, interdisciplinary, team-based cancer research (inclusive of T0 to T4) that involves investigators from University of Tennessee Health Science Center (UTHSC), with West Cancer Center (WCC) and University of Arkansas for Medical Sciences (UAMS), which will give rise to future external funding. The Awards are designed to promote new lines of research and are not intended as bridging funds or a mechanism to extend ongoing funded research.

- **Minimum Requirements:** To be eligible for a UTHSC/UAMS CORNET Award in Cancer, each proposal must include, **at minimum,** one faculty member from UTHSC with one faculty member from UAMS.
- **Award Level**: Resources are available to fund up to three Awards, for up to $50,000/award, for one year. No-cost-extensions will not be approved at year-end.
- **Required Application Materials**: (submit as one pdf file via the UTHSC InfoReady Review (IRR) portal (https://uthsc.infoready4.com)
    1. Face Sheet (template provided; not included in 2-page limit) Include proposal title, and for each PI: name, degree, academic title, campus, college, department and contact information.
    2. Abstract (200-word limit; not included in 2-page limit)
    3. Research proposal (**2 pages only** - please include: specific aims, background and significance, preliminary data and a brief description of methods)
    4. References (not included in 2-page limit)
    5. Description of extramural grant proposals that will be submitted as a result of this seed money. Please include funding agency and submission due date (one paragraph, not included in 2-page limit)
    6. Budget (template provided; one page for each campus; not included in 2-page limit)
        a. Faculty salaries are not allowed. Limited salaries are allowed for students, post docs and staff (small % effort for technicians, students and post docs).
        b. Budget maximum is $25,000 for each campus
        c. No travel money
    7. Information regarding other support for each PI (intramural and extramural). Please include: title, funding agency, grant type, project period, annual direct costs.
    8. NIH style Biosketch for each investigator (5-page limit for each investigator)
    9. Templates for Face Sheet and Budget Page, along with an Applicant Checklist (to ensure a complete submission package) can be downloaded from the IRR competition page.
- **Institutional Approvals:** Institutional approvals for research involving human subjects, animals, biohazards, etc. must be received prior to release of funding.
- **Application Deadline:** Submissions are due by **Tuesday, June 27, 2017**. Funding decisions will be made by 8/1/17 and funding for selected grants will begin on 9/1/17. **Applications will only be accepted via the UTHSC InfoReady Review Portal.** Directions for using the portal can be found on the UTHSC InfoReady Review homepage.
- **Review**: Submitted proposals will be reviewed by a committee, chosen by the UTHSC and UAMS Vice Chancellors for Research.
- A year-end progress report will be due in both Offices of Research, at the close of the grant.

For questions about this funding opportunity, contact either Lisa Youngentob, Director-Research Development, **lyoungen@uthsc.edu** or Linda Williams, Research Liaison-Office of the Vice Chancellor for Research, **ldwilliams@uams.edu.**

Speaker Abstracts

“Clinical Advances in Hormone Receptor Positive (HR+) Breast Cancer”

Dr. Lee Schwartzberg
Professor of Medicine
Chief, Division of Hematology/Oncology
The University of Tennessee Health Science Center
Executive Director
West Cancer Center

The majority of breast cancers express estrogen receptors and/or progesterone receptors, which are responsible for cell signaling promoting the cancer phenotype of growth, invasiveness, metastases and anti-apoptosis. Endocrine therapy designed to inhibit hormone receptor activity has long been a mainstay of treatment for advanced HR+ breast cancer. Recent advances in understanding the biology of this signaling, including cross-talk with other relevant pathways such as the cell cycle and the PI3K-mTOR pathway, has led to clinical trials of targeted therapies designed to inhibit various elements of the signaling cascade. Our group has been extensively involved in these studies which have resulted in a number of drugs being approved and licensed by the FDA for use in advanced HR+ breast cancer, while other agents remain in promising trial opportunities.

The selective estrogen receptor downregulator/degrader, fulvestrant, is a first-in-class agent that has recently demonstrated superiority as monotherapy compared to the prior standard, aromatase inhibition, in the treatment of newly metastatic HR+ breast cancer. New classes of agents have exploited the observation that cross-pathway signaling increase is a major cause of resistance to endocrine monotherapy and has led to the concept of combination therapy designed to inhibit two pathways simultaneously in an effort to improve clinical response. Combinations of an endocrine therapy such as an aromatase inhibitor or fulvestrant combined with cell cycle blockade achieved by inhibiting the activity of the cyclin dependent kinases 4/6 have shown dramatic improvement in progression-free survival in advanced HR+ breast cancer. Our enrollment to phase I- III clinical trials of the CDK 4/6 inhibitors have contributed to approval of these agents. Other combinations of endocrine therapy with mTOR inhibitors have demonstrated clinical benefit as well and are currently used in the clinic. With a portfolio of multiple new combinations, our clinical trial focus has turned to optimizing the proper sequence and combinations for patients.

Another HR+ related resistance mechanism in breast cancer is the androgen receptor pathway. Research at UTHSC has helped clarify the role of this receptor in breast cancer. Our group has been active in clinical trials utilizing both androgen receptor inhibitors and selective androgen receptor modulators in AR+HR+ breast cancer. Preliminary results are encouraging and are the focus of multiple investigations. The presentation will discuss the evolution of therapies for HR+ advanced breast cancer emphasizing recent and ongoing clinical trials utilizing CDK 4/6 inhibitors and AR inhibition.

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"Overview of Cancer Research at the Winthrop P. Rockefeller Cancer Institute"
Dr. Peter D. Emanuel
Director, Winthrop P. Rockefeller Cancer Institute
Professor of Medicine
The University of Arkansas for Medical Sciences

The Winthrop P. Rockefeller Cancer Institute on the UAMS campus is a fully matrixed organization meaning that all faculty have primary appointments in departments in various colleges across UAMS and then secondary appointments in the Cancer Institute. This allows the Cancer Institute to engage its research activities across the entire UAMS campus. The top priority for the Cancer Institute in the near term is to obtain designation by the National Cancer Institute (NCI), which is accomplished via being awarded a P30 Cancer Center Support Grant from NCI. The main recurring theme of NCI designation is that NCI Cancer Centers are expected to foster and encourage collaboration and interaction. Prior to submitting a P30 grant application the NCI expects, and our External Advisory Board agrees, that we should have $18-20 million annually in direct costs in cancer-related grants, and that roughly half of this amount should be coming directly from NCI grants. The NCI also expects that the investigators holding these grants should be divided amongst 3-4 thematic research programs. One of the programs is expected to be a program in cancer control, cancer prevention, or population sciences. The NCI also expects that we will have developed robust core facilities and shared resources to assist our funded scientists with their investigations. There are also specific criteria and metrics with regards to our cancer clinical protocols. Finally, we will be scrutinized as to whether the Rockefeller Cancer Institute meets the six essential characteristics of a cancer center. In Dr. Emanuel's presentation, he will elaborate on these aspects of becoming a NCI-designated cancer center, as well as areas where further interaction and collaboration with scientific partners in the geographic area may be helpful.

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"Comorbidity Factors Associated with Human Papillomavirus Infectivity: Implications in Cervical Cancer Health Disparity"
Dr. Subhash C. Chauhan
Professor
Departments of Pharmaceutical Sciences and Department of Pathology
The University of Tennessee Health Science Center

Objective: High-risk strains of human papillomavirus (HPV) cause cervical cancer (CxCa). Certain underserved populations in the United States, such as American Indian and African American women disproportionately suffer from CxCa compared to their Caucasian counter parts. However, precise etiology and comorbidity factors associated with CxCa health disparity are not fully uncovered. In this study, we have investigated the molecular interplay existing between various comorbidity which are primarily known for the progression of CxCa.

Method: To define a molecular association of smoking, alcohol and HIV co-infection, HPV infected CxCa cells (Caski and SiHa) were treated with a smoking carcinogens Benzo[a]Pyrene (BaP) or alcohol (EthOH) or both. Effects of these treatment was analyzed on tumorigenic phenotypes and the expression of HPV E6/E7 was determined by qRT-PCR, immunoblotting and confocal microscopy. The effect of HIV co-infection on the expression of HPV E6/E7 was also investigated by incubating CxCa cells with conditioned media derived from HIV infected monocytic cells.

Results: Exposure of BaP or EthOH or their combination enhances the expression of HPV E6/E7 oncogenes thus induces oncogenic phenotypes. These cofactors in presence of HIV co-infection augment the expression of HPVE6/E7 oncogenes. These cofactors alter cellular oxidative stress via modulation of the expression of PRDX6 enzyme. Interestingly, curcumin and its nanoparticle formulation (Nano-Cur) effectively inhibit BaP/EthOH induced expression of E6/E7 oncogenes and tumorigenic characteristics of CxCa cells.

Conclusions: The study suggests a molecular link between smoking, alcohol and HIV infection with HPV infectivity and their potential association with CxCa health disparity. These events however, can be effectively attenuated by curcumin/nano-curcumin treatment, implying its role in CxCa prevention/treatment to effectively reduce CxCa health disparity.

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"Translational Drug Development: Research that Takes You from Bench to Bedside and Beyond"

Dr. Hong-yu Li
Professor of Medicinal Chemistry and Chemical Biology
Arkansas Research Alliance Scholar
Helen Adams & Arkansas Research Alliance Endowed Chair
College of Pharmacy
Co-Director of Therapeutics Sciences Program- Winthrop P. Rockefeller Cancer Institute
The University of Arkansas for Medical Sciences

Therapeutic Sciences program at UAMS stems from consideration of the natural affinity of its members interested in the application of translational approaches to cancer therapy, coupled with the mechanistic basis for the action of such therapies, and is led by Drs. Thomas Kieber-Emmons and Hong-yu Li. The program puts an emphasis on the development and maintenance of innovative practices to strengthen the translational research endeavors.

Low-hanging drug targets have been heavily exploited and potential for target breakthroughs is rare. To excel in an inundated market, Dr. Li's lab generate 'smart-drugs' that are capable of shutting down multiple pathways that promote human disease. Instead of drug-repurposing, we have established the concept of 'target-repurposing'. We identify drug targets that display cooperation in a variety of disease states. We then generate highly advanced candidates to shut down these targets in a balanced fashion. The technique we employ is called SynMedChem, which is derived from synergistic medicinal chemistry. A few examples from Bench to Bedside and beyond will be presented.

Dr. Li is an ex-pharma researcher, having spent 10 years at Eli Lilly and Company as a team leader in medicinal chemistry. Dr. Li has discovered two drugs that are in Phase II clinical trials and one drug that is closing to the market approval. Dr. Li has started two companies from academic research programs.

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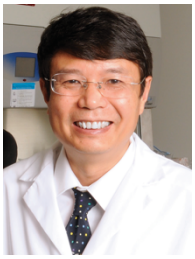

“Targeting Senescent Cells to Improve Cancer Therapy”

Dr. Daohong Zhou
Professor and Deputy Director- Division of Radiation Health
Dept. of Pharmaceutical Sciences, College of Pharmacy
Winthrop P. Rockefeller Endowed Chair for Leukemia Research
Associate Director for Basic Research- Winthrop P. Rockefeller Cancer Institute
The University of Arkansas for Medical Sciences

Cellular senescence, a state of permanent proliferative arrest and altered function, plays an important role in tumor suppression, as well as in embryonic development and tissue repair early in life -- when senescence cells (SCs) are produced transiently and can be easily removed, presumably by the immune system. However, with aging and after cancer cytotoxic therapy, SCs accumulate in many tissues. Whether this accumulation is due to increased production of SCs and/or a decrease in immunosurveillance is not known. Recently, SCs have emerged as significant drivers of aging and age-related diseases, ranging from cancer to cardiovascular disease, neurodegeneration, osteoarthritis (OA), idiopathic pulmonary fibrosis (IPF) and sarcopenia. They are also play an important role in mediating radiation- and chemotherapy-induced normal tissue injury and promoting tumor relapse and metastasis. Consequently, SCs are now attractive targets for therapeutic interventions not only to reduce or delay aged-related diseases and extend health span but also to mitigate cancer therapy-induced normal tissue injury and inhibit tumor relapse and metastasis. We will discuss some of those new progresses in the development of senolytic drugs that can selectively kill SCs and their potential applications for cancer and age-related diseases.

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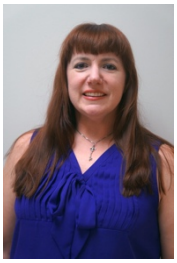

“Highlights of Women’s Basic/Pre-clinical Cancer Research at UTHSC: Opportunities for Collaboration”

Dr. Tiffany N. Seagroves
Associate Professor of Pathology
Executive Director, Molecular Resource Center of Excellence
Associate Vice Chancellor for Research—Research Cores
The University of Tennessee Health Science Center

Women’s cancers are a key focus area in the basic, translational and clinical cancer research programs at UTHSC. Both UTHSC and the West Cancer Center have strong track records in the funding and conduct of basic and clinical research, particularly in breast cancer, and increasingly in ovarian cancer. Research strengths include understanding the molecular determinants of disease, creating and developing novel therapeutic approaches, identifying prognostic, diagnostic and therapeutic biomarkers, and examining the impact of health disparities on patient outcomes. A large proportion of the breast cancer research program is devoted to understanding the etiology and treatment of triple-negative breast cancers, with investigators focusing on dissecting the contributions of multiple pathways that drive tumor aggressiveness and therapeutic resistance, including the classic hormone receptors (ER, PR and AR), dysregulated signaling pathways such as NF-κB, HIF and Wnt, and other factors, such as dysregulated micro-RNA expression. Expertise is available in several technical areas, including developing novel patient-derived xenograft (PDX) models, longitudinal animal bio-imaging, viral vector development, delivery and genetic modification of cell lines or PDX models, rational drug design, drug development and pre-clinical drug testing, cancer stem-like cell biology and genome-wide analysis of drivers of cancer phenotypes. The women’s cancer group is comprised of faculty from multiple departments and Colleges, providing a wide range of scientific expertise. Research accomplishments from several faculty who are affiliated with the basic/pre-clinical

research programs in women's cancers at UTHSC, and who are members of the West Cancer Center, will be overviewed to stimulate future collaborations.

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"Cancer Prevention and Population Sciences Program at the UAMS Winthrop P. Rockefeller Cancer Institute"

Dr. L. Joseph Su
Co-director, Cancer Prevention and Population Sciences Program- Winthrop P. Rockefeller Cancer Institute
Professor, Department of Epidemiology, Boozman College of Public Health
The University of Arkansas for Medical Sciences

By virtually any definition, Arkansas is a rural state with a greater percentage of the population living in rural areas than the nation in general. Many of the characteristics of rural communities, such as percentage of minority population, lower socioeconomic status, lack of access to screening programs or health care, obesity, and environmental exposures, are generally associated with cancer health disparity. Thus, a main goal of the Cancer Prevention and Population Sciences Program at the Winthrop P. Rockefeller Cancer Institute is to develop research to understand the etiology of cancer specific to the populations we serve, with an emphasis on defining those components underlying health disparities in the urban-rural continuum. The efforts for this program will be directed toward understanding the underlying cause of cancer health disparity through population-based research and community outreach efforts in underserved populations to identify cancer etiologic factors unique to Arkansas, implementing effective preventive strategies in reducing the incidence of cancer, and early diagnosis of cancer to reduce cancer burden and associated mortality. To accomplish our goals, it will be necessary to establish an infrastructure to support transdisciplinary research projects that includes investigators with expertise in epidemiology, population-molecular science, behavioral sciences, health policy, recruitment and retention of study participants, and interaction with community members and community health providers. The specific aims for the Cancer Prevention and Population Sciences are to 1) reduce cancer incidence by identifying etiology (molecular) and risk (environmental, social, and cultural) factors as well as developing and implementing novel strategies/interventions to reduce cancer risk; 2) promote early cancer detection by increasing the adoption and implementation of recommended cancer prevention and control services; and 3) develop and test immune-mediated interventions for preventing cancers and recurrence of cancers as well as reducing progression of cancers in a watchful waiting state.

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"HPV, Epigenomics and Anal Cancer"

Dr. David Shibata
Scheinberg Endowed Chair in Surgery
Professor and Chair, Department of Surgery
The University of Tennessee Health Science Center
Deputy Director
West Cancer Center

Although squamous cell carcinoma of the anus, an HPV-associated malignancy, is a relatively rare cancer, it is one of a handful of malignancies for which the incidence has continued to rise significantly over the past 3-4 decades in the United States. High-risk populations have been identified; however,

optimal screening and preventions strategies have yet to be firmly established. The treatment of anal cancer has evolved with primary chemotherapy and radiation being the first-line treatment for locoregionally-confined disease. Despite relatively favorable response rates, the treatment remains associated with significant toxicity and strategies to improve the therapeutic index would be valuable. There is emerging interest in the interplay between HPV infection and host genome methylation as mediators of both carcinogenesis and tumor behavior. Our experience with the applications of whole genome methylation analysis in screening and treatment-related biomarker development for anal cancer and other HPV-associated cancers will be presented.

POSTERS

(1) "PSMA ANTIBODY FUNCTIONALIZED DOCETAXEL-LOADED MAGNETIC NANOPARTICLES FOR PROSTATE CANCER THERAPY"

Prashanth K.B. Nagesh[1], Nia Johnson[1], Vijaya K.N. Boya[1], Pallabita Chowdhury[1], Aditya Ganju[1], Bilal Hafeez[1], Sheema Khan[1], Stephen W. Behrman[2], Meena Jaggi[1], Subhash C. Chauhan[1], Murali M. Yallapu[1]*

[1]Department of Pharmaceutical Sciences and Center for Cancer Research, [2]Department of Surgery, University of Tennessee Health Science Center, Memphis, TN

Objectives: Prostate cancer (PrCa) is the second most leading cause of cancer-related death in men in the United States. Chemotherapy (Docetaxel, Dox) is currently the most common first-line therapeutic option. However, adverse side effects and chemo-resistance of docetaxel limits its clinical use. Improving docetaxel targeted delivery and its activity at the tumor site using a targeted nanoparticle system could be an attractive strategy for PrCa therapy. Prostate Specific Membrane Antigen (PSMA) is highly overexpressed in PrCa cells, thus is a highly attractive molecular target for PrCa therapy. In this study, we developed and determined anti-cancer efficacy of a novel docetaxel loaded, PSMA targeted magnetic nanoparticle (PSMA-MNP-Dox) formulation for PrCa therapy.

Methods: Docetaxel loaded magnetic nanoparticle (MNP-Dox) formulation is composed of an iron oxide core coated with cyclodextrin (for drug loading) and F127 polymer (for particle stability and chemosensitization). Therapeutic efficacy of this unique nanoparticle formulation was evaluated using clinically relevant cell line models (C4-2, PC-3, and DU-145) through cell proliferation and colony formation assays. Molecular effects of this formulation on apoptosis, anti-apoptosis, and drug resistance associated proteins were evaluated using immunoblotting assays. Contrast imaging property of MNP-Dox formulation was examined using Phantom Gel MR imaging model. For active targeting, PSMA antibody conjugation to this formulation was achieved through N-hydroxysuccinimide group containing PEG polymer. Active targeting potential of this formulation was evaluated in PSMA+ (C4-2) and PSMA– (PC-3) cell lines, C4-2 generated tumor xenografts.

Results: MNP-Dox formulation showed optimal particle size and zeta potential which can efficiently internalized in PrCa cells. Our formulation showed anti-cancer efficacy in prostate cancer cell lines. Additionally, it induces the expression of apoptosis associated proteins, Bax and Bad, cleaved PARP, and caspase 3, and down-regulated the expression of anti-apoptotic proteins, Bcl-2 and Bcl-xL. Moreover, it also inhibited the expression of chemo-resistance associated proteins (PSMA and MDR1). Our PSMA antibody targeted MNPs-Dox formulation exhibited a profound uptake pattern in PSMA+ cells (C4-2) compared to PSMA null (PC-3) cells, suggesting its targeting potential. A similar targeting potential was also observed in ex-vivo studies while using C4-2 tumor xenografts, however, no intense targeting was observed in normal tissues due to lack of PSMA expression.

Conclusion: PSMA antibody functionalized MNP-Dox formulation can efficiently target PSMA + PrCa cells and deliver docetaxel into prostate tumors. This targeted drug delivery system could reduce the dose of docetaxel required to kill cancer cells, thus minimizing long-term docetaxel associated systemic toxicity and drug-resistance.

(2) "NANO SELF-ASSEMBLIES OF PACLITAXEL FOR BREAST CANCER TREATMENT"

Prashanth Kumar Bhusetty Nagesh[1], Pallabita Chowdhury[1], Sumeet S. Chauhan[2], Elham Hatami[1], Sheema Khan[1], Bilal Hafeez[1], Subhash C. Chauhan[1], Meena Jaggi[1], Murali M. Yallapu[1]

[1]Department of Pharmaceutical Sciences and Center for Cancer Research, University of Tennessee Health Science Center, Memphis, TN
[2]Houston High School, Germantown, TN

Objectives: Breast cancer (BC) is second leading cause of cancer-related deaths in the United States. Paclitaxel (PTX) is an FDA-approved and frequently used chemotherapeutic agent against various cancers, including BC. However its adverse side effects and chemo-resistance against it, limits its use in the clinic. Minimizing the toxicity issues of PTX through nanoparticle technology (such as PTX bound to human serum albumin nanoformulation, i.e., Abraxane®) is feasible and has displayed encouraging outcomes. With this background, we aim to generate PTX self-assemblies (PTX-SAs) using various biocompatible polymers and surfactants, and to evaluate its efficacy against BC cells.

Methods: PTX-SAs composed of PTX dispersion or a core formation with a polymer at a weight ratio of 1:50. The extent of PTX assembly/binding efficiency was determined using a fluorescence quenching study. FT-IR spectral study was employed to confirm the presence of PTX in PTX-SAs. The optimal polymers for forming PTX-SAs were identified through measurement of particle size, zeta potential and TEM. Another check point of generating a better PTX-SAs was evaluated by its extent of cellular internalization in BC cells and through hemolytic assay. Finally, the finalized PTX-SAs were examined for in vitro activity in BC cells using proliferation, colony formation, and immunoblotting assays.

Results: We screened 22 biocompatible polymers for PTX-SAs formation, out of which 8 were finalized due to excellent PTX binding profiles, appropriate particle size ranges (40-300 nm), zeta potentials (-14.0 to -4.0 mV), and superior internalization in BC cells. The optimized PTX-SAs exhibited enhanced anti-cancer capability in MCF7 and MDA-MB-231 BC cells in proliferation and colony formation assays, compared to free PTX. This was further affirmed through tubulin stabilization studies. Further, PTX-SAs treatment in BC cells demonstrates a distinct induction of the expression of apoptosis-associated proteins and distinct downregulation of anti-apoptotic proteins.

Conclusion: Overall this study suggests a simple and feasible PTX self-assembly approach for achieving superior anti-cancer activity with PTX.

(3) "MIR-205 REPLENISHMENT IN PROSTATE CANCER CELLS: A NOVEL NANOPARTICLE APPROACH"

Prashanth K.B. Nagesh[1], Pallabita Chowdhury[1], Vijayakumar N. Boya[1], Vivek K. Kashyap[1], Sheema Khan[1], Bilal B. Hafeez[1], Nadeem Zafar[2], Stephen W. Behrman[3], Subhash C. Chauhan[1], Meena Jaggi[1], Murali M. Yallapu[1]

[1]Department of Pharmaceutical Sciences and Center for Cancer Research, [2]Department of Pathology, [3]Department of Surgery, University of Tennessee Health Science Center, Memphis, TN

Introduction: Prostate cancer (PrCa) is the most common male malignancy among men in the United States. Recent studies suggest that low expression of miR-205 is seen in PrCa cell lines and tumors in comparison to normal prostatic epithelial cells. A number of studies have shown that restoration of miR-205 in PrCa cells resulted in suppression of cell growth, epithelial-to-mesenchymal transition, and chemosensitization. However, due to the poor pharmacological kinetics and low in vivo stability

of miR-205, limitations are being experienced at the clinical level. Therefore, we have chosen a novel nanoparticle-based approach to deliver miR-205, for improved therapeutic benefits in PrCa.

Methods: A novel miR-205 nanoparticle formulation (named miR-MPG) was generated which is composed of an iron oxide core layered with polyethyleneimine (PEI), and NHS-PEG-NHS (PEG) polymer. The miR-205 withholding and release characteristic of miR-PEG were examined through fluorescence quenching and agarose gel electrophoresis. Hemocompatibility of this formulation was examined using a hemolysis assay. Cellular uptake of miR-MPG formulation was evaluated using flow cytometry and confocal studies. Further, therapeutic and chemosensitization activity of miR-205 were assessed using cell-culture based assays. Molecular effects associated with the PrCa cells growth inhibition were evaluated through protein profiling and qRT-PCR analyses.

Results and Discussion: miR-MPG formulation exhibited optimal particle size and zeta potential, which are suitable for cancer therapeutics. Agarose gel electrophoresis binding studies suggested 5 μg of nanoparticle formulation is optimum to hold 1 μg of miR-205 mimic. Release of miR-205 from miR-MPG was determined with respect to concentration of anionic molecules and in a time-dependent manner. We observed no hemolysis during miR-MPG interaction with the red blood cells indicating its hemocompatibility. In addition, miR-MPG particles exhibited superior internalization and endosomal escape in PrCa cells. This formulation displayed enhanced sensitization of PrCa cells to docetaxel. Additionally, it induced the expression of apoptotic proteins (Bax, Bim, cleaved PARP, and caspase 3), and downregulated the anti-apoptotic proteins (Bcl-2 and survivin). Moreover, the expression of the chemoresistance-associated protein MDR1 was profoundly inhibited in cells treated with miR-MPG in the presence of docetaxel. Further dataset of qRT-PCR studies showed induced expression of the miR-205 and affected the expression of its downstream genes. These results suggest that miR-205-MPG formulation may serve as an ideal delivery vehicle to deliver miR-205.

Conclusion: Results from this study suggests that successful delivery of miR-205 through miR-MPG nanoparticles can induce sensitization potential for docetaxel treatment. This novel therapeutic modality might be effective for PrCa patients undergoing chemotherapy.

(4) "ORMELOXIFENE SUPPRESSES THE GROWTH OF PROSTATE TUMOR VIA INHIBITION OF β-CATENIN INDUCED AR SIGNALING"

Aditya Ganju, Bilal Bin Hafeez, Mohammad Sikander, Vivek K Kashyap, Murali M Yallapu, Subhash C Chauhan, Meena Jaggi

Department of Pharmaceutical Sciences, Cancer Research Center, University of Tennessee Health Science Center, Memphis, TN

Background: Prostate cancer (PrCa) first manifests as an androgen-dependent disease and can be treated with androgen-deprivation therapy. Despite the initial success of androgen ablation therapy, resistance to anti-androgen therapy displays by progression to hormone refractory (androgen-independent) advanced stage PrCa which is primary cause of patient's death. Main underlying cause for the onset of hormone refractory cancer is ligand independent activation of AR signaling in PrCa cells. It has been shown that β-catenin acts as a non-androgen activator of AR which enhances AR transactivation in PrCa cells. Thus, identification of agents with excellent pharmacokinetics and pharmacodynamics parameters that can inhibit ligand independent activation of AR signaling might be highly useful for the treatment of advanced stage PrCa. Herein, we identified a synthetic molecule, ormeloxifene (ORM), which efficiently represses β-catenin mediated ligand independent activation of AR signaling, thus, inhibits growth and metastatic features of PrCa cells.

Methods: Androgen-refractory but AR positive PrCa cell (C4-2) was used as an in vitro and in vivo model systems. Effect of ORM on AR and PSA protein levels was determined by Western blot analysis. Effect of ORM treatment was analyzed on AR and PSA luciferase activities by transiently transfecting the C4-2 cells by AR and PSA luciferase plasmids. Renilla construct was used as an internal control. C4-2 cells nuclear and cytoplasmic lysates were prepared using Active Motif kit. Immunoprecipitation analysis was performed to determine if ORM inhibits physical interaction of β-catenin with AR. Therapeutic efficacy of ORM was evaluated in cell lines and PrCa xenograft mouse models.

Results: ORM dose-dependently (10, 15 and 20 μM) inhibited the protein levels of AR and its downstream target protein PSA. ORM (10 and 20μM) treatment also inhibited AR transactivation as determined by decreased promoter activities of AR and its target gene PSA. ORM (10 and 20μM) treatment inhibited protein levels of nuclear β-catenin and physical interaction of β-catenin with AR in PrCa cells. ORM administration dose- dependently (intra-peritoneal; 100 and/or 500μg/mouse; thrice/week) significantly ($P<0.01$) inhibited growth of C4-2 cells derived xenograft tumors in athymic nude mice. ORM treatment significantly ($P<0.01$) inhibited the expressions of nuclear AR and β-catenin expressions in xenograft tumor tissues. These ORM treated mice did not show any apparent toxicity in our study.

Conclusion: Our study demonstrates that ORM is a potent inhibitor of β-catenin-mediated activation of AR signaling. Based on its safety profile, ORM might be an ideal candidate for repurposing to treat advanced stage PrCa alone or in combination with other therapies.

(5) "ATTENUATION OF PANCREATIC TUMOR GROWTH BY A SMALL MOLECULE TUBULIN INHIBITOR"

Vivek K Kashyap, Bilal B. Hafeez., Qinghui Wang, Saini Setua, Aditya Ganju, Murali M. Yallapu, Duane D. Miller, Wei Li, Meena Jaggi, Subhash C. Chauhan

Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN

Introduction: Pancreatic cancer (PanCa) is one of the most fatal cancers and is ranked as the fourth common cause of cancer-related deaths among both men and women in the US. The management of PanCa is exceptionally difficult due to the extremely poor response to available chemotherapeutic drugs. Microtubules are dynamic structures composed of α–β-tubulin heterodimers that are essential in cell division and are important targets for several clinical drugs (paclitaxel, docetaxel and vinblastine). However, clinical use of these tubulin targeting drugs have toxicity and drug resistance issues in cancer patients. Thus, identification of more potent non-toxic inhibitors of β-tubulin is urgently required for cancer therapy purposes. In this study, we have identified a synthetic compound (ABI-231) which is a potent inhibitor of β-tubulin, and evaluated its therapeutic efficacy against PanCa in vitro and in vivo model systems.

Methods: ABI-231 ((2-(1H-indol-3-yl)-1H-imidazol-4-yl)(3,4,5-trimethoxyphenyl))-methanone was synthesized and characterized in our department. Effect of ABI-231 on proliferation, migration and invasion of human PanCa cells (ASPC1, HPAFII, and PANC1) was performed by in vitro functional assays (MTS, wound healing, and Boyden chamber). Effect of ABI-231 on the expression of β-tubulin isoforms was determined and compared with other clinical inhibitors of β-tubulin by Western blot, and qRT-PCR. Moreover, effect of ABI-231 on the expression of β-tubulin III in PanCa cells was determined by confocal microscopy. Therapeutic efficacy of ABI-231 against PanCa was evaluated in an ectopic xenograft mouse model.

Results: ABI-231 treatment inhibited cell proliferation, invasion, migration and colony formation ability of PanCa cells in a dose-dependent manner (1-100 nM) compared to vehicle treated group. Aberrant expression of β--tubulin III is involved in aggressiveness and drug resistance of various type of cancers including PanCa. ABI-231 effectively inhibited the protein levels and mRNA expression of total β--tubulin (TBB), TBB1, TBB2C, TBB3 and TBB4 in PanCa cells via destabilization. Our confocal microscopy results further showed inhibition of β-tubulin in ABI-231 treated PanCa cells. ABI-231 also inhibited the mRNA expressions of β-tubulin III in these PanCa cells. Upregulation of micro RNA 200c (miR-200c) has been shown to inhibit the expression of β-tubulin III in cancer cells. ABI-231 treatment of PanCa cells showed significant ($P<0.01$) induction of miR-200c as determined by qRT-PCR. ABI-231 administration (intra-tumoral; 50 μg/mouse), three times/week significantly ($P<0.01$) inhibited the growth of ASPC1 cells derived xenograft tumors in athymic nude mice.

Conclusion: Taken together, our results suggest that ABI-231 is a potent β-tubulin inhibitor and chemotherapeutic agent which could be used for the treatment of pancreatic cancer.

(6) "MUC13 INDUCED NFκB ACTIVATION REGULATES METABOLIC REPROGRAMING BY PROMOTING ITS CROSSTALK WITH GLUT-1 RECEPTOR"

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Objective: Pancreatic cancer (PanCa) is the fourth most common cause of cancer-related deaths in the US. MUC13, mucin is aberrantly expressed in PanCa and promotes tumor growth and progression. Herein, we investigate the fundamental role of MUC13 in glucose metabolism and delineate the molecular interplay of various molecules governing MUC13 mediated metabolic reprograming that may be involved in pancreatic tumor maintenance.

Methods: MUC13 expressing (Panc-1) and knockout PanCa cells (HPAF-II) were generated for the study. Immunoblotting and qRT-PCR assays were performed to assess the expression of protein and mRNA levels, respectively, of key signaling molecules involved in glucose metabolism of PanCa. MUC13 and Glut-1 interaction was studied using reciprocal coimmunoprecipitation, immunofluorescence, proximity ligation, Western blotting, cocapping assays in cell lines. Lactate and glucose assays were performed using commercially available kits. In vitro functional assays using wound healing scratch assay (migration), and cell Matrigel assay (invasion) were performed in presence or absence of Lactate and 2DG supplementation.

Results: Our results demonstrate that MUC13 expression leads to the TNF-induced activation/nuclear translocation of NFκB p-65 and phosphorylation of IkB which in turn upregulates additional key proteins, Glut-1, c-MYC, Bcl-2. This recruits the Glut-1 to MUC13, wherein MUC13 functionally interacts with Glut-1 and stabilizes it, initiating downstream events that result in altered glucose metabolism. MUC13 expression in PanCa cells increases glucose uptake, lactate secretion which is reduced on MUC13 knockdown. Additionally, MUC13 mediates increased cell migratory and invasion potential which can be potentiated by supplementing the culture media with lactate, an end product of aerobic glycolysis. However, treatment of cells with NFκB inhibitor, Sulfasalazine, inhibits the MUC13 and Glut-1 interaction and abrogates all these events associated with glucose metabolism.

Conclusion: These results suggest that MUC13 plays an important role in metabolic reprogramming of PanCa cells metabolism to induce cancer growth and enhanced cellular invasion and motility. NFκB acts downstream of MUC13 to coordinate the events leading to its interation with Glut-1 and metabolic

reprogramming. Overall, these findings illustrate mechanisms by which MUC13 coordinates the shift in metabolism to sustain cancer growth and invasion in PanCa.

(7) "MUC13 IS INVOLVED IN TRAIL RESISTANCE IN PANCREATIC CANCER"

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Background: Pancreatic cancer (PanCa) is a third leading cause of cancer related deaths in US due to late diagnosis and development of chemo-resistance. Therefore, understanding molecular mechanisms that confer survival benefit to PanCa cells may offer new therapeutic strategies for PanCa treatment. Mucin, MUC13 is aberrantly expressed in PanCa, promoting cancer growth and progression and these effects are abrogated by microRNA-145 (miR-145) restoration. Unlike other cancer types, PanCa is highly resistant to Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) that emerges as one of the most-promising experimental cancer therapeutic drugs. Herein, we demonstrate the integration of novel approach to overcome chemo-resistance and offer TRAIL-based therapeutic strategies.

Methods: MUC13 expressing and null stable PanCa cells were generated to investigate the role of MUC13 in cell survival. miR-145 mimics were used to investigate the effect of MUC13 silencing in promoting survival and inhibiting apoptosis in presence of TRAIL using Western blotting, cell proliferation (MTT), Acridine orange staining and flow cytometry apoptosis assays (cell cycle, Annexin V/7AAD staining). Various distinct domain specific constructs of MUC13 were constructed such as the mucin (α), Beta (β) sea urchin sperm protein enterokinase arginine (SEA) domain and cytoplasmic (CD) domains and transfected into MUC13 null Panc-1 cells to identify the role of different domains in eliciting survival benefit to PanCa cells.

Results: Results demonstrate that MUC13 expression blocks activation of caspase-8 and death receptor mediated apoptosis in PanCa cells in response to TRAIL treatment as observed through Western blotting and flow cytometer. Inhibition of MUC13 using shRNA knockdown or miR-145 restoration resulted in TRAIL mediated increase in apoptotic cell death as evidenced by AnnexinV/7AAD and sub G0 population, as well as rendered PanCa cells sensitive to treatment with drugs, such as paclitaxel. Additionally, cells treated with TRAIL in combination with pactitaxel or abraxane showed enhanced apoptosis on inhibition of MUC13 expression using miR-145 restoration. Further investigation showed that cytoplasmic domain of MUC13 (MUC13-CD) is indispensable for blocking caspase-8 activation and PARP cleavage, indicating that the MUC13-CD blocks TRAIL-induced signaling upstream to Bid by inhibiting caspase-8 activation.

Conclusion: These observations suggest that MUC13 contributes to the survival advantage in PanCa cells in response to treatment with drugs or death inducing ligands such as, Tumor-necrosis factor-related apoptosis-inducing ligand (TRAIL) which can be strategically overcome by miR-145 replenishment. These findings indicate that MUC13 silencing sensitizes PanCa cells towards TRAIL therapy and counteracts chemo-resistance mechanisms in PanCa that may lead to novel combination therapies for PanCa treatment.

(8) "TARGETED DRUG DELIVERY USING A NOVEL ANTI-MUC13 CONJUGATED NANOPARTICLES FOR PANCREATIC CANCER"

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Pancreatic cancer (PanCa) survival rate is poor due to late diagnosis. Patients with metastatic PanCa usually receive chemotherapy that causes various adverse effects due to their side effects on normal cells. Therefore, the tumor specific delivery of drugs is highly desired. A recently identified mucin, MUC13 is aberrantly expressed in pancreatic tumors but not in normal pancreas. Due to its high membrane expression, MUC13 may serve as an excellent target for PanCa treatment. Here in, we present a strategic development of nano-formulation (MUC13-MNP) using magnetic nanoparticles (MNP) conjugated to novel, in-house generated, anti-MUC13 monoclonal antibodies (MAbs) that can recognize MUC13 in pancreatic tumors in its native confirmation. The conjugation and stability of anti-MUC13 MAbs to MNP is achieved using PEG-NHS linker forming a stable, non-reducible covalent bond as determined by agarose gel electrophoresis. Our results demonstrate that the formulation exhibits an optimal particle size and zeta potential, and enhanced cellular uptake and internalization in HPAF-II (MUC13(+)) compared to Panc-1 (MUC13(-)) cells. This was determined by flow cytometer, Prussian blue staining and immunofluorescence experiments. In order to investigate their therapeutic efficacy, MUC13-MNPs were used to deliver an anticancer molecule, curcumin (CUR), a natural derivative of Curcuma longa to improve its pharmacokinetics/bioavailability. Interestingly, MUC13-MNP-CUR resulted in sustained delivery of CUR, enhanced inhibition of PanCa cell proliferation, migration and invasion and induced apoptosis in MUC13 (+) compared to MUC13(-) PanCa cells. Therefore, the results indicate high therapeutic significance of MUC13-MNPs for achieving pancreatic tumor specific delivery of drugs.

(9) "HIF-1-DEPENDENT REGULATION OF CREATINE KINASE METABOLISM PROMOTES BREAST CANCER INVASION AND METASTASIS"

Hilaire Playa Barch, Danielle L. Peacock Brooks, Raya Krutilina, Luciana P. Schwab, Deanna Parke, and Tiffany N. Seagroves

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Dysregulated tumor cell metabolism is a hallmark of cancer progression and therapeutic resistance. In a screen for Hypoxia-Inducible Factor (HIF)-dependent genes regulating metabolism, we identified creatine kinase, brain isoform (CKB) as down-regulated in HIF-1 knockout mammary tumor cells. Creatine kinases (CKs) reversibly catalyze the transfer of a high-energy phosphoryl group from ATP to creatine, generating phosphocreatine in the forward reaction, and ATP in the reverse reaction. CKs are up-regulated in a variety of solid tumors, including ovarian, breast, colon, lung and brain. Knockdown of CKB in the polyoma middle T (PyMT) transgenic mouse model of metastatic breast cancer suppressed the production of intracellular ATP and invasion in vitro, and inhibited metastasis from the mammary gland to the lung in vivo.

CK activity is known to be inhibited by cyclocreatine, a creatine kinase substrate that represses CK-dependent generation of ATP from phosphocreatine. When female FVB/Nj mice were injected with wild type PyMT cells in a tail vein assay and then treated with cCr (1g/kg/day, IP), lung metastasis was repressed to the same extent as Ckb gene knockdown. Moreover, when cCr therapy was administered 7 days after tail vein injection, cCr was effective in preventing the transition of lung micrometastases to macrometastases. To explore the role of CK activity in regulating cell proliferation, survival in suspension, cellular metabolism and invasion, we next created CKB loss- and gain-of-function models using human breast cancer cell lines, and compared phenotypes to cCr treatment. Whereas deletion

of CKB had no effect on cell proliferation or survival in adherent conditions or in suspension, either deletion of CKB or cCr therapy potently reduced ATP levels and invasive potential in vitro. Preliminary data also indicate that co-treatment of triple negative breast cancer cell lines with cCr sensitizes cells to doxorubicin. Together, these data suggest that inhibition of CK activity may be effective in treating stage IV breast cancer. We are currently testing whether cCr has anti-metastatic efficacy as a monotherapy, or in combination with conventional chemotherapies, using luciferase-labeled patient-derived xenograft (PDX) models.

(10) "OPTIMIZING METASTATIC BREAST CANCER PATIENT-DERIVED XENOGRAFT (PDX) MODELS FOR BIO-IMAGING AND PRE-CLINICAL STUDIES"

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Purpose: To generate sub-lines of PDX models of metastatic breast cancer representing the common molecular sub-types of breast cancer that express firefly luciferase 2 (Luc2), using parental PDX lines that were originally developed at the Huntsman Cancer Institute (HCI, DeRose et al., Nature Med. 2011). Luciferase-labeling facilitates bio-imaging of tumor-bearing animals during longitudinal pre-clinical studies to track tumor progression and metastasis qualitatively (location of signal) and quantitatively (light flux, photons of light/sec).

Methods: Several early-passage PDX models representative of triple negative breast cancer (TNBC: estrogen receptor, ER-, progesterone receptor, PR- and HER2-unamplified), or HER2+ and ER+/PR+ (HER2-) breast cancer patients were obtained from Dr. Welm (HCI), including HCI-1 (TNBC), HCI-2 (TNBC), HCI-7 (ER+/HER2+), HCI-9 (TNBC), HCI-10 (TNBC) and HCI-11 (ER+/HER2-). The parental PDX lines from HCI were expanded in Nod/Scid/Gamma (NSG) females at UTHSC. Regenerated tumor tissue was digested and tumor cells were genetically modified ex vivo using lentiviruses that express Luc2-puromycin. A variety of cell culture conditions and media formulations were tested to optimize viability of cells in culture and luciferase labeling. Following successful transduction, Luc2+ cells were injected with growth-factor reduced Matrigel into the cleared inguinal mammary fat pads of recipient NSG females (Luc2+, P0 generation). P0 Luc2+ tumors were then expanded by transplanting 2 x 2 mm tumor fragments into the next generation of NSG recipients (P1). For each HCI-Luc2+ model, the rate of tumor growth and the ability to detect metastatic lesions was measured over time and at study endpoint, which also included ex vivo imaging of dissected organs. In addition, passageable cell line models were derived from the HCI PDX Luc2+ lines to perform either drug response assays or additional genetic modifications (gene knockout by CRISPR, for example) in vitro.

Results: Bio-imaging of live mice bearing PDX specimens facilitates tracking of primary tumor growth and metastases concomitantly over time and the detection of metastatic lesions during ex vivo imaging of dissected organs. Since 2012, our lab has generated five new Luc-2 labeled HCI PDX lines, including 4 TNBCs: HCI-2-Luc2, HCI-10-Luc2, HCI-1-Luc2, and an androgen receptor (AR)+ TNBC line, HCI-9-Luc2, and one ER+/HER2+ line, HCI-7-Luc2. These models have been shared with multiple investigators at UTHSC, the HCI and internationally. The models have been used for pre-clinical studies that either validate data generated in conventional breast cancer cell lines, or to test drug efficacy of novel compounds using bio-imaging as one readout, resulting in several publications and manuscripts in revision.

Future studies: Samples from parental, early passage Luc2+, and later passage Luc2+ PDX tumors, or cell lines generated from these PDX models, will be sent to Dr. Welm for RNA-seq and copy number

variant (CNV) analysis to confirm that they have not significantly genetically drifted from the original patient specimen.

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(11) "A POPULATION-SPECIFIC VARIANT IN RB1 ASSOCIATED WITH BASAL-LIKE BREAST CANCER"

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Racial disparity in breast cancer mortality has been recognized for decades and persists despite advances in early diagnosis and treatment. Notably, African American (AA) women have a lower breast cancer incidence, but a higher breast cancer death rate, than European American (EA) women. Breast cancer incidence and mortality vary by tumor molecular subtypes defined by gene expression patterns. Basal-like breast cancer (BLBC), which accounts for ~75% triple-negative breast cancer (ER-/PR-/Her2-), is usually diagnosed at early age and associated with poor prognosis. Compared to other ethnic groups (i.e., EA, Asians and Pacific Islander women), AA women are more likely to have BLBC. This study is aimed to investigate whether population-specific, detrimental SNPs contribute to AA-BLBC. We analyzed exome sequencing data from the Exome Aggregation Consortium (ExAC) to identify non-Synonymous SNPs with higher minor allele frequency (MAF) in African-ancestry population than other ethnic groups (Cutoff setting: MAF of African-ancestry >1% and three fold higher than other ethnic groups). To select candidate SNPs that likely increase BLBC risk for AA women, the SNPs specific for African-ancestry population were filtered to include SNPs located in genes targeted for somatic alterations in BLBC according to the Cancer Genome Atlas (TCGA) database and predicted to have high impact on protein function by using the SIFT and PolyPhen-2 functional annotation programs. This analysis led to the identification of ~3000 candidate SNPs (hosted by 1758 genes) that are specific for African-ancestry population and likely have significant functional impact on breast cancer-related genes. To validate our findings from data analysis, TagMan allelic discrimination SNP assays were performed to examine the prevalence of 11 candidate SNPs in a panel of AA breast cancer patients. We found that a SNP in the tumor suppressor retinoblastoma 1 (RB1) is associated with early age at diagnosis of AA-TNBC.

(12) "THE NOT4 UBIQUITIN LIGASE UTILIZES AN EVOLUTIONARILY CONSERVED RNA BINDING DOMAIN TO MAINTAIN PROTEOSTASIS AND REGULATE RNA POLYMERASE II TRANSCRIPTION"

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The Ccr4-Not complex is a multiprotein complex highly conserved from yeast to humans that regulates every aspect of the RNA polymerase II (Pol II) transcribed mRNA lifecycle, as well as ribosomal RNA synthesis by RNA polymerase I. The core subunit Not4, which is an E3 RING domain ubiquitin ligase, also functions to regulate global proteostasis by controlling the assembly and function of the proteasome. Human Ccr4-Not is essential for the regulation of embryonic stem cells, and Ccr4-Not core subunits are found to be either mutated or overexpressed in a wide-variety of cancers, including

leukemia and cancers of the breast, colon, and prostate. How the Not4 ligase contributes to such diverse cellular functions necessary for cell growth and proliferation is unclear. To address this issue and its potential relevance to cancer, we have utilized a yeast model to specifically assess the role of the candidate RNA binding domain (the RNA recognition motif, RRM) in maintaining proteostasis and Pol II transcription. We demonstrate that Not4 requires this domain in vivo, and that mutations in highly conserved RRM residues predicted to disrupt its function cause sensitivity to proteostatic stress and global ubiquitin homeostasis. These results suggest this RNA binding domain is required for proteasome regulation. Utilizing high throughput RNA sequencing (RNA-seq), we demonstrate that cells expressing a Not4 RRM mutant selectively upregulate genes required for ribosomal biogenesis and nutrient stress responses, implicating RNA binding in vivo as required for Not4 to control Pol II transcription involved in cellular biosynthetic activity. Furthermore, we demonstrate that the Not4 RRM domain regulates interactions between the Ccr4-Not holocomplex and Pol II, suggesting Not4 RNA binding in vivo is critical for controlling the Pol II transcription cycle. Because the yeast and human Not4 ubiquitin ligases share identical domain architecture, this study suggests that the human Not4 will likely regulate similar processes that contribute to cancer when deregulated.

(13) "CONSTITUTIVE ACTIVATION OF STAT3 AND NF-KB SIGNALING IN GLIOBLASTOMA CANCER STEM CELLS REGULATES THE NOTCH PATHWAY"

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Despite aggressive surgery and treatment, patients with the most common primary adult brain tumor, glioblastoma (GBM), have a median survival of only ~15 months, and a 5-year survival rate of less than 5%. These malignant glial tumors remain a serious clinical and scientific problem. While dysregulated cell proliferation, differentiation, migration and cell death play critical roles in many cancers, the underlying molecular events remain poorly understood in GBM. GBMs are comprised of multiple cell types that express both neuronal and glial markers, as well as a small subpopulation of GBM stem-like cells (GSCs) that have high tumor-initiating capacity and are highly resistant to therapies. Therefore, new therapeutic strategies that target GSCs are desperately needed to improve patient survival. In this study, we describe a novel relationship between glioblastoma CSCs and the Notch pathway, which involves the constitutive activation of STAT3 and NF-kB signaling. Glioma CSCs were isolated and maintained in vitro using an adherent culture system, and the biological properties were compared with the traditional cultures of CSCs grown as multicellular spheres under nonadherent culture conditions. Interestingly, both adherent and spheroid glioma CSCs show constitutive activation of the STAT3/NF-kB signaling pathway and up-regulation of STAT3- and NF-kB-dependent genes. Gene expression profiling also identified components of the Notch pathway as being deregulated in glioma CSCs, and the deregulated expression of these genes was sensitive to treatment with STAT3 and NF-kB inhibitors. This finding is particularly important because Notch signaling appears to play a key role in CSCs in a variety of cancers and controls cell fate determination, survival, proliferation, and the maintenance of stem cells. The constitutive activation of STAT3 and NF-kB signaling pathways that leads to the regulation of Notch pathway genes in glioma CSCs identifies novel therapeutic targets for the treatment of glioma.

(14) "VINCRISTINE-INDUCED DEATH IN G1 PHASE IS BLOCKED BY CDK4/6 INHIBITION IN PRIMARY ACUTE LYMPHOBLASTIC LEUKEMIA CELLS"

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Microtubule targeting agents (MTAs), such as vincristine, are important anticancer agents and are thought to act primarily in mitosis. However, there is increasing evidence that MTAs can also cause death in interphase, and that this may be the major mechanism in the clinical setting especially for slow-growing tumors. We have recently discovered that when primary acute lymphoblastic leukemia (ALL) cells are treated with vincristine, cells in G1 phase die directly without advancing to other phases of the cell cycle. This system represents a powerful model for understanding interphase mechanisms of MTA action, and provides an opportunity to test whether MTAs can be combined with agents that target interphase processes in order to create novel treatments for ALL. One such candidate is palbociclib (PCB), a highly selective inhibitor of cyclin dependent kinases 4/6 (CDK4/6), whose activity is necessary for the transition from G1 to S phase. PCB has been shown to cause G1 phase arrest in cancer cell lines such as glioblastoma. In this study we tested the effect of palbociclib alone or in combination with vincristine in primary ALL cells and in T98G and HeLa cell lines as controls. We discovered that ALL cells pretreated with PCB were completely refractory to vincristine. This effect was reversible, and when PCB was removed from cell arrested in G1 phase by PCB, sensitivity was restored. However, PCB did not block death induced by the Bcl-2 inhibitor, ABT-263. These results suggest that G1 phase microtubules are essential for the survival of ALL cells and provide information important for selection of rational and effective drug combinations for ALL.

(15) "INDICATORS OF RESPONSIVENESS TO IMMUNE CHECKPOINT INHIBITORS"

Shields BD, Mahmoud F, Taylor EM, Byrum SD, Sengupta D, Koss B, Baldini G, Ransom S, Cline K, Mackintosh SG, Edmondson RD, Shalin S, Tackett AJ.

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Modulation of the immune system can produce anti-tumor responses in various cancer types, including melanoma. Recently, immune checkpoint inhibitors (ICI), in single agent and combination regimens, have produced durable and long-lasting clinical responses in a subset of metastatic melanoma patients. These monoclonal antibodies, developed against CTLA-4 and PD-1, block immune-inhibitory receptors on activated T-cells, amplifying the immune response. However, even when using anti-CTLA-4 and anti-PD-1 in combination, approximately half of patients exhibit innate resistance and suffer from disease progression. Currently, it is impossible to predict therapeutic response. Here, we report the first proteomic and histone epigenetic analysis of patient metastatic melanoma tumors taken prior to checkpoint blockade, which revealed biological signatures that can stratify patients as responders or non-responders. Furthermore, our findings provide evidence of mesenchymal transition, a known mechanism of immune-escape, in non-responding melanoma tumors. We identified elevated histone H3 lysine (27) trimethylation (H3K27me3), decreased E-cadherin, and other protein features indicating a more mesenchymal phenotype in non-responding tumors. Our results have implications for checkpoint inhibitor therapy as patient specific responsiveness can be predicted through readily assayable proteins and histone epigenetic marks, and pathways activated in non-responders have been identified for therapeutic development to enhance responsiveness.

(16) "WNT10B/b-CATENIN SIGNALING INDUCES HMGA2-EZH2-DRIVEN LUNG METASTASIS VIA EPIGENETIC MODULATION IN CHEMORESISTANT TNBC"

Peter Wend, Ikbale El Ayachi, Iram Fatima, Stephanie Runke, Julio Silva, Joseph Kerby Gray, Chidi Zacheaus, Ding Xiangming, Christopher Sistrunk, Jasmine Miller-Kleinhenz, Wendy Silva, Stephan Lehr, Andrew C. White, Robert Cardiff, Raya Krutilina, Lisa D. Yee, Lily Yang, Ruth M. O'Regan, Tiffany N. Seagroves, William E. Lowry, Victoria Seewaldt, Susan A. Krum and Gustavo A. Miranda-Carboni

Triple-negative breast cancers (TNBC) are active for Wnt10b/b-catenin/Hmga2 signaling, mediating a highly aggressive metastatic outcome. Wnt10b/b-catenin-trackable tumor initiating cells (CD44hiCD24-) are responsible for visceral metastasis, express elevated HMGA2, and have the classical hallmarks of EMT. HMGA2 ablation blocks tumor initiation and metastasis. We uncovered a novel protein-protein interaction between HMGA2 and EZH2 that is essential for transcriptionally active b-catenin/TCF4/LEF-1 nuclear core complexes, which are essential for tumor growth and metastasis in vivo. In the absence of HMGA2 or EZH2, we observed loss of cMYC and VIMENTIN, epigenetic alteration of both histone methylation and acetylation with concurrent accumulation of the tumor suppressor BRCA1. Chemical inhibition of Wnt signaling in TNBC PDX tumors abolishes visceral metastasis in vivo, with concurrent loss of cMYC, VIMENTIN, EZH2 and highly-chemoresistant CD44+ cells co-expressing HMGA2 and AXIN2. Clinical samples reveal that expression of WNT10B, HMGA2 and EZH2 precede the development of tumors in women at high risk for metastatic TNBC and it is predictive of poor-survival outcome.

(17) "RACIAL DISPARITIES IN SURVIVAL OUTCOMES AND BREAST TUMOR SUBTYPES AMONG AFRICAN AMERICAN WOMEN IN MEMPHIS, TENNESSEE"

GREGORY VIDAL[1,2], ZORAN BURSAC[1], GUSTAVO MIRANDA-CARBONI[1], SHELLEY WHITE-MEANS[1], and ATHENA STARLARD-DAVENPORT[1]

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Background: Racial differences in breast cancer survival outcomes between African American (AA) and non-Hispanic white women in the United States has been well documented. Memphis, TN has the worst racial disparity gap in breast cancer survival outcomes among AA women compared to white women and when compared to 50 of the largest US cities. Whether or not these racial differences may be attributed to differences in breast tumor subtype and treatment is unknown. Therefore, we investigated the extent to which racial disparities are associated with breast tumor subtypes and treatment outcomes. Methods: A total of 3527 patients diagnosed with stage I to IV breast cancer between January 2002 to April 2015 at Methodist Health hospitals and West Cancer Center in Memphis, TN were included in the analysis. Kaplan-Meier survival curves were generated and Cox proportional hazards regression was used to compare survival outcomes among 1342 (38.0%) AA and 2185 (62.0%) white breast cancer patients by race and breast tumor subtype. Results: Over a mean follow-up time of 29.9 months, AA women displayed increased mortality risk [adjusted hazard ratio (HR), 1.65; 95% confidence interval (CI), 1.35–2.03] and were more likely to be diagnosed at advanced stages of disease. AA women with TNBC had the highest death rate at 26.7% compared to white women at 16.5%. AA women with TNBC and luminal B/HER2- breast tumors had the highest risk of mortality. Regardless of race, patients who did not have surgery had over 5 times higher risk of dying compared to those who had surgery.

(18) "TRANSLATION OF AN EVIDENCE-BASED WEIGHT LOSS MAINTENANCE INTERVENTION FOR RURAL, AFRICAN AMERICAN ADULTS OF FAITH: DESIGN OF THE WORD (WHOLENESS, ONENESS, RIGHTEOUSNESS, DELIVERANCE)"

Karen Yeary, Jerome Turner, Page Moore, C. Heath Gauss, Carol Cornell, Elaine Prewitt, Mick Tilford, Kimberly Harris

Background: The positive effects of weight loss on obesity-related risk factors diminish unless weight loss is maintained. Yet little work has focused on the translation of evidence-based weight loss interventions with the aim of sustaining weight loss in underserved populations. Using a community-based participatory approach (CBPR) that engages the strong faith-based social infrastructure characteristic of rural African American communities is a promising way to sustain weight loss in African Americans, who bear a disproportionate burden of the obesity epidemic. Objectives: Led by a collaborative community-academic partnership, The WORD aims to change dietary and physical activity behaviors to produce and maintain weight loss in rural, African American adults of faith. Design: The WORD is a randomized controlled trial with 425 participants nested within 30 churches. All churches received a 16-session core weight loss intervention. Half of the churches will be randomized to receive an additional 12-session maintenance component. Methods: The WORD is a cultural adaptation of the Diabetes Prevention Program, whereby small groups are led by trained church members. Participants have been assessed at baseline, and 6 months, and will be assessed at 12, and 18 months. A detailed cost-effectiveness and process evaluation will be included.

Summary: The WORD aims to sustain weight loss in rural African Americans. The utilization of a CBPR approach and the engagement of the faith-based social infrastructure of African American communities will maximize the intervention's sustainability. Unique aspects of this trial include the focus on weight loss maintenance and the use of a faith-based CBPR approach in translating evidence-based obesity interventions.

(19) "CULTURAL ADAPTATION OF DIABETES SELF-MANAGEMENT EDUCATION FOR U.S. RESIDING MARSHALLESE"

Karen H. Kim Yeary, Nia Aitaoto, Karra Sparks, Mandy Ritok-Lakien, Jonell S. Hudson, Peter Goulden, Wiliamina Bing, Sheldon Rikon, Jelleson Rubon-Chutaro, Pearl Mcelfish

Background: Type 2 diabetes (T2D) is a significant public health problem, with U.S. Pacific Islander communities—such as the Marshallese—bearing a disproportionate burden. Using a community-based participatory approach (CBPR) that engages the strong family-based social infrastructure characteristic of Marshallese communities is a promising way to manage T2D. Objectives: Led by a collaborative community-academic partnership, the Family Model of Diabetes Self-Management Education (DSME) aimed to change diabetes management behaviors to improve glycemic control in Marshallese adults with T2D by engaging the entire family. Design: To test the Family Model of DSME, a randomized, controlled, comparative effectiveness trial with 240 primary participants was implemented. Half of the primary participants were randomly assigned to the Standard DSME and half were randomly assigned to the Family Model DSME. Both arms received ten hours of content comprised of 6-8 sessions delivered over a 6-8 week period. Methods: The Family Model DSME was a cultural adaptation of DSME, whereby the intervention focused on engaging family support for the primary participant with T2D. The Standard DSME was delivered to the primary participant in a community-based group format. Primary participants and participating family members were assessed at baseline and immediate post-intervention, and will also be assessed at 6 and 12 months.

Summary: The Family Model of DSME aimed to improve glycemic control in Marshallese with T2D. The utilization of a CBPR approach that involves the local stakeholders and the engagement of the

family-based social infrastructure of Marshallese communities increase potential for the intervention's success and sustainability.

(20) "THE ABSENCE OF WnT10b EXPRESSION INHIBITS TUMOR INITIATION AND METASTASIS MODULATING STROMA-TUMOR MICROENVIRONMENT HOMEOSTASIS"

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Visceral metastasis to the brain, bone, liver and lung are the cause of about 45,000 deaths of breast cancer patients per year in the USA. Triple-negative breast cancer (TNBC) has the worst survival outcome and the greatest incidence of metastasis. Wnt10b signaling is active in TNBC and predictive of survival outcome, but its underlying mechanisms on stromal cells remain unknown. Therefore, we questioned what role Wnt10b plays in stromal cells in the tumor microenvironment of the mammary gland? Transgenic MMTV-Wnt10bLacZ (Wnt10bLacZ) primary mammary gland tumors give rise to rare lung metastases and are phenotypically identical to human TNBC expressing extracellular matrix (ECM) markers: CD146, Tenascin C, Periostin and several matrix metalloproteinases (MMPs). Primary Wnt10bLacZ-driven tumor cells do not grow when transplanted into mammary glands of Wnt10b-knockout mice (WKO) in contrast to the wild type (w.t.). Moreover, lung metastatic (LM) cells from Wnt10bLacZ-driven tumors injected into mammary gland of WKO mice do not give rise to secondary LM foci at the same rate than w.t. mice. Backcrossing WKO with Wnt10bLacZ mice illustrate a haplotype insufficient phenotype, heterozygous Wnt10b mice have delay in tumor onset and WKO mice block tumor formation by >80%. Mechanistically, we show that stroma-derived and epithelial cells isolated from WKO mammary gland differentially regulate gene responses altering the normal epithelial-stromal homeostasis. We provide evidence that loss of Wnt10b alters ECM and MMPs proteins and the loss of a single WNT-ligand (Wnt10b) alters the tumor's "seeding" potential and affects the "soil" to block tumor formation and/or metastasis. We suggest that Wnt10b is essential to educate the stromal cells to mitigate tumor initiation and metastatic colonization.

(21) "WNT INHIBITOR ICG-001 PREVENTS VISCERAL METASTATIC TRIPLE NEGATIVE BREAST CANCER IN A CHEMO-RESISTANT PATIENT DERIVED XENOGRAFT -PDX-MODEL"

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Triple negative breast cancer (TNBC) is characterized by absence of the estrogen receptor and progesterone receptor, and human epidermal growth factor receptor 2 amplification. Such cancers are highly aggressive and frequently metastasize to the lung and brain. Unlike other breast cancer subtypes such as, ER+, PR+ and/or HER2+, TNBCs have no specific targeted-therapeutics; therefore, studies should be directed for development of targeted therapies to treat this condition. Recent studies indicate that Wnt/β-catenin signaling is particularly activated in TNBC and is associated with reduced overall survival in all patients. Therefore, pharmacological targeting of Wnt signaling pathway constitutes an ideal approach for treating TNBC and various Wnt inhibitors are currently in use in clinical trials, such as; ICG-001 in metastatic colon cancer. The inhibitory effects of ICG-001 have not been tested in chemoresistant TNBC PDX tumors. Herein, we report for the first time that ICG-001 compound selectively inhibited the growth of several European American (EA) and African American

(AA) triple negative breast cancer subtypes MSL and BSL-1 cell lines both in vitro and in vivo models. To further investigate the precise mechanisms of action in the regulation of Wnt/β-catenin signaling by ICG-001, we performed Western blot analysis, apoptosis assays, cell cycle assays and quantitative real-time reverse transcriptase- polymerase chain reactions in human triple negative breast cancer cells. This compound significantly interfered with Wnt/β-catenin signaling, and its inhibition led to downregulation of important downstream targets such as Axin2, HMGA2, PCNA, c-myc and Cyclin D1, which in turn led to inhibition of proliferation, cell cycle progression and metastasis confirming our previous results too. In addition ICG-001 inhibited the invasion and motility of tumor cells and showed inhibition and prevention of visceral metastatic PDX tumors from both chemoresistant EA AA women. These results indicate that the Wnt inhibitor ICG-001 could constitute a powerful new chemotherapeutic agent against triple negative breast cancer.

(22) "USE OF A WEB-BASED APP TO IMPROVE BREAST CANCER SYMPTOM MANAGEMENT AND AROMATASE INHIBITOR ADHERENCE: A PILOT RANDOMIZED CONTROLLED TRIAL"

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Background: For postmenopausal women with hormone receptor-positive breast cancer, use of aromatase inhibitors (AI) significantly reduces the risk of cancer recurrence and improves survival, but many patients are nonadherent due to adverse side effects. We conducted a pilot randomized controlled trial of a web-enabled application (app) to provide real-time symptom monitoring between visits and facilitate management of treatment-related adverse symptoms among patients with hormone receptor-positive breast cancer and a new AI prescription.

Methods: Patients were randomized into two groups: (1) App+Reminder: had access to the app and received weekly reminders via text or email to use it, or (2) App: had access to the app but did not receive reminders. The app asked patients about their AI use in the last 7 days and about new symptoms related to the treatment. New symptoms with severity in a clinically-relevant range or AI nonadherence triggered email alerts to the patient's providers. The main analyses compared AI adherence and changes in quality of life.

Results: We enrolled 44 patients, 21 in the App+Reminder and 23 in the App group; 83% of patients approached agreed to participate, 23% were African-American, and 32% were over the age of 65. Overall, 74% of participants in the App+Reminder group used the app at least once per week compared with 38% in the App group ($p<0.01$). Reported AI adherence 8 weeks after initiation was significantly higher among those in the App+Reminder group compared with the App group (100% vs. 72%, $p=0.01$). Using a differences-in-differences analysis, we found that the decrease in quality of life 8 weeks after AI initiation was substantially larger, but not statistically significant, in the App group compared with App+Reminder (difference=7.6, $p=0.191$).

Conclusions: Use of a web-enabled app to provide real-time monitoring of AI adherence and treatment-related symptoms with weekly reminders significantly improves short-term AI adherence and may limit reductions in quality of life. If short-term gains in adherence persist, this low-cost intervention could improve survival outcomes for women with hormone receptor-positive breast cancer.

(23) "MATERIALS FOR PERSONALIZED 3D PRINTED HIGH DOSE RATE BRACHYTHERAPY APPLICATORS"

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Objectives: To study the feasibility of using printable polymers and polymer-metal mixtures for 3D printed applicators designed to fit patient anatomy and to modulate high dose rate brachytherapy ionizing radiation distributions.

Methods: Currently, brachytherapy treatments are based on applicators with simple geometries and dose distributions are computed using a cylindrical symmetry approximation. Consequently, brachytherapy lacks the capability of delivering highly modulated and conformal dose distributions. Our solution is the design and implementation of 3D printed applicators based on patient anatomy utilizing variable material composition to modulate the delivered dose distribution using controlled directional attenuation. We have performed initial printing tests with several materials to determine the stiffness, deformability, radiation attenuation, and stability after multiple autoclave cycles. The tested materials were also evaluated for their biocompatible properties.

Results: The ABS-tungsten mixture, polyurethane and Nylon 680 are desirable because of their physical characteristics. Nylon 680 is a very stable autoclavable polymer, polyurethane is very flexible and can conform to complex patient skin geometries, and ABS-tungsten is an excellent attenuator. Nylon 680 and polyurethane are biocompatible; however, ABS-Tungsten must be enclosed using Nylon 680 for biocompatibility. For these three materials, we identified the optimal extruder and printer bed temperatures to achieve submillimeter printing resolution. A first prototype of a flexible skin applicator, a Valencia applicator, and an autoclavable vaginal cylinder were successfully printed and their dosimetric characteristics are under evaluation.

Conclusions: We identified printing parameters for 3D printable materials that are excellent candidates for skin and intracavitary brachytherapy applicators. We have also demonstrated the feasibility of using 3D printed materials with embedded attenuators to modulate the dose delivered to a malignancy.

(24) "METHIONINE DEPRIVATION POTENTIATES THE EFFECTS OF LOCAL RADIOTHERAPY"

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Methionine dependency is a commonly observed feature of tumor cells, characterized by an impaired remethylation pathway that results in cell death in the absence of methionine. Combination of dietary methionine deprivation (MD) with radiotherapy may have potential in the treatment of tumors, but could be significantly limited by MD-induced toxicity during the long course of radiotherapy. Recent advances in radiotherapy significantly decreased the length of treatment, making the use of short-term MD adjunct therapy possible, while avoiding negative health impacts. In this study, we investigated the effects of dietary MD in the highly metastatic murine B16-F10.1 melanoma model in combination with a single 10 Gy irradiation. We report here that dietary MD alone has an effect on tumor progression equal to a single exposure to 10 Gy, resulting in a greater than 2-fold tumor growth delay. MD significantly potentiated the effects of irradiation as demonstrated by a greater than 3-fold delay in tumor growth in comparison with MD or local irradiation alone. Immunohistochemical examination revealed significantly increased necrosis in tumors treated with MDD and X-rays compared with MDD alone or X-rays alone. Gene expression analysis revealed the involvement of the

Ripk3 interactors Glul and Pygl, as well as the Mag/Ngfr signaling pathway in these differential necrotic responses. Gross and immunohistochemical examination revealed only one non-invasive lung metastasis, despite an increased survival time. Therefore, MD may also suppress tumor metastasis. Our findings suggest that MD holds substantial potential to be used in conjunction with short-course, high dose radiotherapy for cancer.

(25) "BISPHENOL A INDUCES SOX2 IN ER + BREAST CANCER STEM-LIKE CELLS"

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Bisphenol A (BPA) is an endocrine disrupting compound used in food and beverage plastic containers and has been shown to increase breast cancer cellular proliferation. However, the concentrations of BPA used in these experiments are far higher than the physiological levels of BPA detected in the human body. We observed in vitro that exposure of MCF-7 cells to physiological concentrations of BPA failed to increase cell proliferation or to induce canonical estrogen-responsive genes (pS2 and progesterone receptor (PR)), in contrast to 17β-estradiol (E2) treatment. However, MCF-7 cells treated with 10 nM BPA induced ALDH1 expression, a marker of human mammary stem cells. When treated with 10 nM BPA, mammospheres derived either from MCF-7 cells, a patient-derived xenograft, or the normal mouse mammary gland exhibited increased size; however, these effects were not observed in MDA-MB-231 mammospheres. Mechanistically, BPA induced SOX2 mRNA and protein in MCF-7 mammospheres, resulting from enhanced CREB phosphorylation, and subsequent binding of pCREB to a SOX2 downstream enhancer. These findings suggest that physiological levels of BPA increase estrogen receptor positive breast cancer tumor maintenance through enhanced cancer stem-like cell activity via direct regulation of SOX2 transcription.

(26) "PRENYLATED STILBENOIDS: POTENTIAL CHEMOPREVENTIVE AND THERAPEUTIC AGENTS FOR BREAST CANCER"

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Breast cancer is a leading cause of death among women worldwide and continues to highlight the urgent need for strategies that effectively reduce incidence of this disease. Compounds that modulate the cannabinoid receptors have been proposed as potential chemopreventive and therapeutic agents for breast cancer. Using a hairy root-based sustainable and scalable bioproduction system, we are producing a diverse array of stilbenoids with potential applications in human health. In particular, we have shown that prenylated stilbenoids can modulate the cannabinoid receptors. Furthermore, purified prenylated stilbenoids and extracts enriched in these compounds show cytotoxicity in breast cancer cells. Interestingly, the prenyl unit appears to enhance the cytotoxicity of these compounds. Current studies focus on elucidating the signaling pathways affected by these compounds in order to advance our understanding of the anticancer mechanism of these natural products.

(27) "ANTI-MMP-9 DNAzyme: A NEW THERAPEUTIC AGENT TO FIGHT CANCER"

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Matrix metalloprotinase-9 (MMP-9) is a member of the matrician family of enzymes that are associated with many pro-oncogenic events such as angiogenesis, proliferation and tumor metastasis. Several inhibitors of MMPs have shown to reduce growth of primary tumor, onset of distant metastases, and even prolong survival of animals with pancreatic, orthotopic colon or liver tumor. Clinical studies have shown that progression-free survival significantly increased in the patients with inoperable gastric cancer using MMP inhibitor, Marimastat. Despite these intriguing results, the substantial side effects associated with the usage of these MMP inhibitors in clinical trials and their lack of specificity has made them less attractive as anti cancer drugs. RNA cleaving DNA based enzyme (DNAzymes) are catalytic oligonucleotides that cleave specific mRNA sequences, resulting in decreased expression of the encoded protein. The advantages of this method over the other types of antisense technology are catalytic activity, in vivo stability, and ease and efficient delivery.

Here, we show that DNAzymes targeting MMP-9 mRNA (AGBD) inhibit MMP-9 protein expression, cell proliferation, and astrocytoma and glioma cell invasion in vitro. In addition, a single intracranial injection of AGBD is sufficient to reduce the size of intracranial C6 and 9L glioma in rats by 60%; and a weekly intratumoral injection reduced the size of mammary tumors generated in a MMTV-PyMT transgenic mouse model by 71%. The tumor reductions correlate with a decrease in the level of MMP-9 in tumor/stroma cells. In situ hybridization in brain and breast tissues demonstrated that they have efficiently taken up the AGBD molecules and that the DNAzyme is stable in these tissues for at least 30 days post-injection. Neurological testing and H&E staining of the normal brain and breast tumor tissue slices suggests that DNAzyme is safe and not associated with significant cytotoxic effects. Given the potential for systemic administration, these results indicate that anti-MMP-9 DNAzyme can be used as a novel therapeutic agent to fight cancer.

(28) "CHURCH-BASED HUMAN PAPILLOMAVIRUS (HPV) EDUCATION"

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Objective: Determine if Faith-Based HPV education is feasible and increases Gardasil vaccination utilization among participants.

Methods: This is a single arm prospective trial. Voluntary participants will be recruited from four Memphis-area churches. Participants will be given a baseline questionnaire regarding risk factors for HPV-related malignancies. A brief lecture followed by a question and answer session will be given at each of the participating churches. Follow up questionnaires at one and six months after the lectures will be given to participants to determine if the educational lectures changed HPV vaccination utilization or perception regarding HPV vaccination. The primray endpoint is completion of Gardasil vaccination series. Secondary endpoints are study dropout rate, questionnaires completed, rate of 1st dose of Gardasil vaccination received, and determining educational and logistical barriers to vaccination. Using the CDC reported 40% rate of vaccination in Tennessee, 172 participants will be required to evaluate if there is a 10% increase in HPV vaccination completion following educational intervention compared to the initial rates determined by the 1st questionnaire ($p = 0.05$, 80% power).

Results: Trial ongoing.

Conclusions: Trial ongoing.

(29) "TETRASPANINS GENE EXPRESSION IN ORAL SQUAMOUS CELL CARCINOMA"

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More than 90% of oral cancer is Squamous Cell Carcinoma (OSCC). Tetraspanins CD9 and CD82 may play roles in OSCC. Objectives: To evaluate TP53 and tetraspanins genes expression in oral cancer cells and tissue, and understand the roles of tetraspanins in oral cancer. Methods: Genes expression in oral cancer tissue and SCC-25(ATCC), CAL27 (ATCC), S-G, GN23 cell lines were quantify using real-time polymerase chain reaction (qRT-PCR). The relative expression was calculated using ΔΔCT method and normalized against housekeeping genes. T-Test was used for statistics. Results: TP53, CD9 and CD82 gene expression were significantly altered in some OSCC cell lines and tissues. Data represent Mean±S.E. of at least 9 replicates. Conclusion: We compared p53 and Tetraspanins in oral cancer SCC-25 and CAL27 cell lines to the normal gingiva GN23 and S-G cell lines for the first time. The alteration of CD9 and CD82 make it very interesting to further explore the protein expression levels, translational regulation, and the roles of tetraspanins in oral cancer.

Keywords: Oral cancer, tetraspanin, CD9, CD82, gene expression

(30) "HrasG12V AND PTEN LOSS COOPERATE IN FOLLICULAR THYROID CANCER PROGRESSION, METASTASIS AND IMMUNE CELL RECRUITMENT"

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Thyroid cancer is the most common endocrine malignancy and incidence rates are on the rise. We have developed novel murine models that recapitulate the progression of thyroid tumors in patients. Here we report that HrasG12V and Pten loss cooperate in the development of aggressive follicular thryoid tumors that metastasize to the lungs. Further, these tumors recruit an immune suppressive tumor microenvironment that likely contribute to pathogenses and metastasis. We believe this immune suppressive micronvironment represents a novel therapeutic opportunity for the treatment of advanced thyroid cancers.

(31) "TRANSARTERIAL CHEMOEMBOLIZATION WITH PARTHENOLIDE IN A RAT LIVER TUMOR MODEL INDUCES TUMOR REGRESSION WITHOUT ANY DETECTABLE LIVER OR SYSTEMIC TOXICITY"

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PURPOSE: In vitro studies and preliminary screening in a rat liver tumor model demonstrated that transarterial chemoembolization (TACE) with the natural drug parthenolide (PTL) was effective for inhibiting the growth of liver tumor cells without intolerable liver toxicity. Consequently, a 24 rat study was initiated to determine if PTL-Lipiodol TACE treatment of Walker 256 rat liver tumors could inhibit tumor growth or induce tumor regression. The efficacy of the PTL-Lipiodol was also compared to that achieved with transarterial embolization (TAE) with Lipiodol only. METHODS: Luciferase expressing, Walker 256- tumor cells were inoculated into the left lateral liver lobe of male Wistar rats. Transarterial

delivery into the tumors was accomplished by catheterizing the gastroduodenal artery and hand guiding the catheter into the left hepatic artery. Tumor-bearing rats were partitioned into three treatment groups: saline, Lipiodol and PTL dissolved in Lipiodol (PTL-Lipiodol: 80 mM PTL). Magnetic resonance imaging (MRI) and bioluminescence imaging were used to monitor and measure tumor growth noninvasively. Animal body weight and liver function blood biochemicals were measured to assess general health and detect toxicity in all 3 groups. Nine days following treatment rat livers were harvested and examined histologically (hematoxylin and eosin (H&E) staining). RESULTS: The PTL-Lipiodol, TACE treated tumors exhibited a slight (10%), average decrease in tumor volume during a 9 day post treatment period while those embolized with saline or Lipiodol only exhibited an average tumor volume increase of 4.5-fold. The MRI images and blood enzyme/biochemical analyses showed no evidence of liver toxicity or systemic toxicity associated with the PTL-Lipiodol TACE treatment, even with such a high, localized concentration of PTL. Histopathology examinations are still ongoing. CONCLUSION: The inhibition of tumor growth by the PTL-Lipiodol treatment was marked and significant ($p= 0.0286$) and can be attributed to the presence of PTL because the Lipiodol only treatment produced no significant decrease in tumor growth compared to that of the control group ($p= 0.037$). The complete inefficacy of the Lipiodol TAE was unexpected, but may be due to the physically small size of the rat liver and the liver tumors. Further investigation into optimizing the efficacy of PTL-Lipiodol TACE is warranted, including using image guidance during TACE to maximize delivery to the tumors.

(32) "MICRORNA PROFILING TO IDENTIFY RACIAL DISPARITIES IN SMOKING RELATED LUNG TUMORIGENESIS"

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African Americans have been reported to have higher rates of lung cancer incidence and mortality than other racial groups in the United States. In this study, we collected stage I primary lung adenocarcinoma and squamous cell carcinoma from patients at the Methodist University Hospital during last 10 years. The smoking history, age-, gender-, histological type, grade-, and stage-matched lung tumor specimen from African American and Caucasian American were compared.

We matched 12 pairs of African American and Caucasian American patients with squamous cell carcinoma. Notably, miR-200b-3p, miR-200a-3p and miR-4286 were upregulated in African American lung tumor tissue, while miR-142-3p, miR-135b-5p and miR-29b-3p were consistently downregulated. Based on these miRNA expression patterns, analysis of information in the TCGA database suggest that lung tumors from African-American (AA) patients likely have the molecular characteristics of primitive lung tumors, while lacking the molecular characteristics of secretory lung tumors. The primitive subtype of lung cancer is associated with poor prognosis, when compared to other subtypes. While the current experiment was done on a well-controlled small cohort patient, further analysis of larger sample is warranted to validate the result.

Notes

Sketchpad

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