UT CORNET Cancer Conference

Nov. 9, 2016

Murfreesboro, Tennessee

UT CORNET Awards
Collaborative Research Network
Proposals in Cancer Research

Purpose: To stimulate innovative, interdisciplinary, team-based research on Cancer (inclusive of T0 to T4) that involves investigators from the University of Tennessee Health Science Center (UTHSC, all campuses), UT Knoxville, UT Chattanooga, UT Institute of Agriculture, UT College of Veterinary Medicine and Oak Ridge National Laboratory (ORNL), that will give rise to future external funding. The Awards are designed to promote new lines of research and are not intended as bridge funds or a mechanism to extend ongoing funded research.

- **Minimum Requirements:** To be eligible for a UT CORNET Award, each proposal must include, **at minimum,** one faculty member from at least two participating Institutions.
- **Award Level**: Resources are available to fund up to two Awards, for up to $50,000/award, for one year. No-cost-extensions will not be approved at year-end.
- **Required Application Materials**:
    - Abstract (200-word limit; not included in 2-page limit)
    - Research proposal (**2 pages only**-please include: specific aims, background and significance, preliminary data, brief description of methods)
    - References (not included in 2-page limit)
    - Description of extramural funding agency and timeframe of extramural proposals that will be submitted as a result of this seed money (one paragraph not included in 2-page limit)
    - Budget (one page for each campus)
        - Restrictions:
            - Limited salaries (small % effort for technicians, students, or post docs)
            - Budget maximum is $25,000 for each campus
            - No travel money
    - Information regarding other support (intramural and extramural). Please include: title, funding agency, grant type, project period, annual direct costs
    - NIH Biosketch or CV for each investigator (4-page limit)
    - Face Sheet (not included in 2-page limit) For each PI, please include: name, degree, academic title, university, college, department and contact information)
- **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 February 1, 2017. Funding for selected grants will begin on April 1, 2017.
- **Review**: Submitted proposals will be reviewed by a committee, chosen by the campus CROs.
- A year-end progress report will be due in the Offices of Research, at the close of the grant.

To be considered for this opportunity, please submit your proposal, in one pdf to:
Lisa Youngentob, Director-Research Development, UTHSC-Memphis lyoungen@uthsc.edu

For questions regarding this funding opportunity, please contact:
Lisa Youngentob, lyoungen@uthsc.edu, 448-1277

Program Outline
Morning Session

10:00am-10:30am	**Arrival - Continental Breakfast**
10:30am-10:40am	**Introduction** Dr. Steven R. Goodman Vice Chancellor for Research The University of Tennessee Health Science Center
10:40am-10:55am	**A Glimpse of Research at The University of Tennessee Medical Center** Dr. John L. Bell Director, The University of Tennessee Medical Center Cancer Institute University of Tennessee Health Science Center, Knoxville University of Tennessee Medical Center
10:55am-11:10am	**Iron Nanoparticles for Theranostics in Glioblastoma Multiforme** Dr. Jacqueline Johnson The University of Tennessee, Knoxville The University of Tennessee Space Institute
11:10am-11:25am	**MonsterPlex: a novel low cost technology to rapidly screen genetic variation and gene expression in breast cancer tumor cells and other malignancies** Dr. Kurt Lamour University of Tennessee Institute of Agriculture
11:25am-11:40am	**Autobioluminescent Cells: A New Tool for Cancer Bioimaging** Dr. Tingting Xu The University of Tennessee, Knoxville
11:40am-12:00pm	**Question & Answer** Session for Talks #1-4
12:00pm-1:30pm	Poster Presentations and Lunch

Program Outline
Afternoon Session

1:30pm-1:45pm	**Development of New Therapeutic Approaches for Pancreatic Cancer Treatment** Dr. Subhash C. Chauhan The University of Tennessee Health Science Center, Memphis
1:45pm-2:00pm	**Interventional and Therapeutic Control of Cancer Development** Dr. Hwa-Chain Robert Wang The University of Tennessee Institute of Agriculture
2:00pm-2:15pm	**Population Pharmacokinetics of Carboplatin in Dogs** Dr.Tomas Martin-Jimenez The University of Tennessee Institute of Agriculture
2:15pm-2:30pm	**The Impact of Physical Inactivity on Breast and Colon Cancer Worldwide** Dr. Gregory W. Heath The University of Tennessee at Chattanooga
2:30pm-2:50pm	Question & Answer Session for Talks #5-8
2:50pm-3:00pm	**Closing Remarks** Dr. Steven R. Goodman Vice Chancellor for Research The University of Tennessee Health Science Center
3:00pm-3:30pm	**Informal Gathering**
3:45pm	**Departure**

Speaker Abstracts

"A Glimpse of Research at The University of Tennessee Medical Center"
Dr. John L. Bell
Director, The University of Tennessee Medical Center Cancer Institute
University of Tennessee Health Science Center, Knoxville
University of Tennessee Medical Center

The University of Tennessee Medical Center is comprised of the University of Tennessee Graduate School of Medicine (GSOM) and University Health System, Inc. Together they work to serve the citizens of East Tennessee and beyond, striving to accomplish a combined mission of healing, education, and discovery. The GSOM serves as the academic arm of our operation, supporting education and discovery programs in all medical specialties except pediatrics. The hospital functions organizationally with 6 Centers of Excellence, one of which is the Cancer Institute.

Today you will hear an overview of some (not all) of the exciting research programs that exist on the Knoxville campus. These programs include basic laboratory research, focusing on amyloidosis, cancer theranostics, drug delivery systems, and new molecular tracer development programs. Translational research programs to be discussed will focus on mechanisms of micro-calcifications in various disease models both in vitro and in vivo and how these programs may collaboratively evolve into clinical application regarding prognostic and therapeutic information. Our clinical research programs to be discussed will include development of pathways which improve outcomes and delivery of various oncologic conditions, lung cancer screening opportunities, and utilization of data analytics for clinical application.

The discussion will focus on collaborative opportunities including but not limited to our medical center campus, the main Knoxville graduate/undergraduate campus, the Oak Ridge National Laboratory, and others.

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"Iron Nanoparticles for Theranostics in Glioblastoma Multiforme"
Dr. Jacqueline Johnson
Associate Professor
Department of Mechanical, Aerospace, and Biomedical Engineering
The University of Tennessee, Knoxville
The University of Tennessee Space Institute

Gliomas are the most common primary tumor, with most of them being malignant and rapidly fatal if untreated. Brain tumors present special challenges for treatment because of their location in proximity to critical neurological structures. Although the ideal goal of treatment with tumors is complete excision, the infiltrating nature of primary tumors and the possibility of damage to critical structures with all tumors often make this an impractical goal. The ability to improve the treatment via hyperthermia and diagnostic yield of magnetic resonance imaging scans would aid in both planning treatments as well as providing valuable prognostic information.

Iron oxide nanoparticles have been developed over many years for hyperthermia (induced by an alternating magnetic field), contrast agents for magnetic resonance imaging (MRI), and drug delivery. However, iron-metal nanoparticles have a higher heat capacity (3 x that of iron oxide) and

magnetization potential as well as potentially inhibiting tumor growth by iron overload (an area of research largely unexplored). Unfortunately, iron metal has traditional problems with biocompatibility, solubility and stability. This can be overcome by passivating the surface with an inert polymer such as polyethylene glycol (PEG). Such a coating assists in keeping the nanoparticles small and allows for future functionalization with bioactive molecules, such as may be useful for uptake in tumors.

Theranostics is the ultimate goal for the iron nanoparticles. We have developed some synthesis routes of iron nanoparticles with an inert and biocompatible coating. Future experiments include measuring temperature increases during hyperthermia, and testing the particles as an MRI enhancement agent. Results and procedures will be presented.

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"MonsterPlex: a novel low cost technology to rapidly screen genetic variation and gene expression in breast cancer tumor cells and other malignancies"

Dr. Kurt Lamour
Professor of Molecular Epidemiology
Department of Entomology and Plant Pathology
University of Tennessee Institute of Agriculture

MonsterPlex is a PCR-based targeted sequencing technology developed by Dr. Kurt Lamour at the University of Tennessee, Knoxville. MonsterPlex provides significant cost reduction when genotyping or genetically profiling thousands of individual samples for 100's of genetic targets. Target regions are usually 60 to 100bp and may contain complex (e.g. clustered) SNPs or INDELS. The technology is organism independent and requires a small amount of DNA (or cDNA) per assay. Most recently, the technology was tested on archival (FFPE) breast cancer tumor tissue to measure gene expression for 80 breast cancer-related genes via targeted sequencing. The pilot study was a success and the purpose of this talk will be to briefly describe the technology and opportunities for collaborative research on cancer.

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"Autobioluminescent Cells: A New Tool for Cancer Bioimaging"

Dr. Tingting Xu
Research Associate
Center for Environmental Biotechnology
University of Tennessee, Knoxville

In vivo optical bioimaging permits the visualization of an optical signal from living cells and tissues to provide a unique perspective toward the understanding of biological processes as they occur within an authentic *in vivo* environment. The light originates from cells genetically programmed to 'report' the presence or activation of specific biological events that can indicate medical diagnostic states. Current toolbox of optical imaging includes luciferases and fluorophores (proteins and small molecules) for bioluminescent and fluorescent imaging respectively. For *in vivo* imaging, the virtually non-existent background luminescence in animal tissues provides a preferably high signal-to-noise ratio for bioluminescent imaging, whereas the sensitivity of fluorescent imaging is inevitably affected by autofluorescent emission from cells and tissues. Bioluminescence-producing cells have to date primarily relied upon the integration of firefly luciferase constructs whose bioluminescent signal is dependent upon the extraneous addition of substrate (luciferin), thereby requiring repetitive animal injections and consequent intermittent snapshots of imaging data. To overcome this obstacle, we

have developed a synthetic luciferase cassette that enables cells to continuously produce a bioluminescent signal without the need for extracellular stimulation. Based on the bacterial luciferase gene cassette of *Photorhabdus luminescens*, this system encodes both a luciferase protein, as well as a short synthetic pathway for transforming natural intracellular products into luciferin substrates. This autobioluminescent system has been validated for its expression across a suite of cell types (kidney, breast, colon, liver, pancreas, and bladder) and demonstrated to self-modulate its output signal concurrent with the host's metabolic activity level. Results from assays employing this autobioluminescent signal therefore correlate strongly with those from existing metabolic activity assay systems (i.e., MTT assays and commercially available firefly luciferase-based bioluminescent assays), but can also be applied towards the dose-responsive correlation of autobioluminescent output with hormone-induced cell proliferation, and dose-dependent autobioluminescence induction in response to specific chemical targets through the use of target-specific genetic controls. Autobioluminecently labeled cancer cells has also been demonstrated to allow for noninvasive tracking of tumor growth and response to drug treatment over time without the need of injecting substrate at each and every time point of interest. This presentation will provide an overview of the autobioluminescent imaging technology and its application in cancer research.

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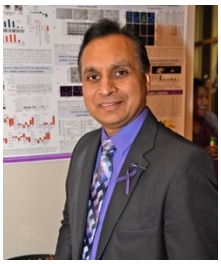

"Development of New Therapeutic Approaches for Pancreatic Cancer Treatment"

Dr. Subhash C. Chauhan
Professor
Departments of Pharmaceutical Sciences and Department of Pathology
University of Tennessee Health Science Center, Memphis

Pancreatic cancer (PanCa), is the fourth leading cause of cancer related deaths in the United States due to the lack of early diagnosis and poor response to available therapeutics. Thus, identification of newer therapeutic approaches that can aid current therapeutics is highly desirable. We have ***defined multidimensional roles of MUC13 mucin in the pathogenesis and therapeutics/imaging of PanCa.*** We have reported that MUC13 is highly expressed in human pancreatic tumors but not in normal pancreas and its expression progressively increases with disease stage and metastasis. MUC13 enhances tumorigenesis through modulation of multiple oncogenes (*HER2, PAK1, ERK,* metastasin/*S100A4, TERT, sonic hedgehog (SHH), GATA-1*) associated with tumorigenesis/metastasis and desmoplasia. We have also observed a functional interaction of MUC13 and HER2 in PanCa cells and identified miR-145 as a tumor suppressor and a novel regulator of MUC13 in PanCa. Additionally, we have identified drugs that inhibit tumor desmoplasia (targets SHH pathway) and enhances therapeutic response of gemcitabine, thus, can be of therapeutic benefit for PanCa. Moreover, we have generated unique anti-MUC13 mouse **monoclonal (MAb)** and **recombinant humanized (HuAb)** antibodies that can efficiently target pancreatic tumors. Furthermore, we have successfully generated multiple patented nanoparticle formulations for antibody guided tumor specific targeted drug delivery and imaging. *Taken together, our* data suggest a crucial role of MUC13 in PanCa pathogenesis. Utilization of a novel anti-MUC13 monoclonal antibody can be used for the targeted tumor specific delivery of novel nanoparticle formulations in pancreatic tumors. This research will establish the multifaceted role of MUC13 in pathogenesis of PanCa and advance diagnosis and therapy of PanCa to reduce the morbidity and mortality caused by this devastating disease.

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“Interventional and Therapeutic Control of Cancer Development”

Dr. Hwa-Chain Robert Wang
Professor of Molecular Oncology
Department of Biomedical and Diagnostic Sciences
College of Veterinary Medicine
University of Tennessee Institute of Agriculture

Over 80% of breast cancers are sporadic. Sporadic cancer development is a multi-year, -step, and -path disease process attributable to long-term exposure to small quantities of environmental carcinogens. However, a dichotomy exists between the way sporadic cancer forms and the way carcinogenesis has been studied. The main-stream doctrine routinely uses high-dose carcinogens to intensively induce malignancy. Recently it is accepted **i)** that the effects of low-dose carcinogens cannot be predicted by the effects observed at high doses; **ii)** that low-dose carcinogens individually may not be able to induce a full course of cellular carcinogenesis to malignancy; and **iii)** that the impact of combined low-dose carcinogens on cellular carcinogenesis should be addressed to understand cancer development. In addition, biologically-disruptive agents, are not recognized carcinogens, with the ability to act adversely on cancer-related mechanisms also contribute to sporadic cancer development. However, the lack of clear low-dose carcinogenic and disruptive agents (**CDAs**) in breast cell carcinogenesis is a serious obstacle in identifying methods for intervening in cancer development. On the other hand, the current main-stream regimens for treating malignant cancer emphasize targeted inhibition of aberrant modulators to regain control of cell growth. However, inhibiting aberrant modulators in cancer cells may indiscriminately inhibit counterpart modulators required for normal cells and induce atypical regulation of rescuing modulators, thereby causing intolerable toxicity, drug resistance, and cancer recurrence. We have been developing a low-dose chronically-induced breast carcinogenesis model and taking a holistic approach of identifying **i)** cancer-involved low-dose CDAs, **ii)** CDA-counteractive preventive agents to intervene in cancer development, and **iii)** pathway-dependent therapeutic agents capable of modulating, not necessarily inhibiting, aberrant pathways to preferentially induce death and reduce resistance of cancer cells. Our research seeks to effectively control sporadic breast cancer development, malignancy, and recurrence towards ultimately improving quality of life for patients.

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“Population Pharmacokinetics of Carboplatin in Dogs”

Dr. Tomas Martin-Jimenez
Associate Professor
Department of Biomedical and Diagnostic Sciences
College of Veterinary Medicine
University of Tennessee Institute of Agriculture

Introduction: Precise dosing of anticancer drugs is difficult due to the proximity between effective and toxic doses. Carboplatin is an anticancer drug commonly used in the treatment of a variety of solid tumors in dogs. The objective of this study was to explore the pharmacokinetics (PK) of this drug in a population of canine oncology patients, with particular attention to the size and sources of PK variability. Materials: This study included 82 cases of dogs treated at our Veterinary Teaching Hospital for a variety of malignancies during a 4-year period. Doses were administered by a 20 min CRI at 200-300 mg/m2 (1-12.5 mg/kg). Blood samples were collected at the start of the infusion and then at several times during the following 8 hours, averaging 5 samples per dog. Samples were analyzed by HPLC. Clinical and demographical covariates were recorded from each case. Data were analyzed using Monolix 4.1.2 Software (Lixoft SAS, Orsay, France). Results: Data were best fit by a

monocompartmental model with zero order input and proportional intra- and inter-individual variability. Population parameter and variability estimates of Vd and Cl were 3.4 L (64% CV) and 57 ml/min (56% CV), respectively. Residual CV was 24.5%. Clearance was correlated with body weight (BW) and body surface area (BSA), but not with age or gender. Volume was correlated with BW, BSA, age and hyperthermia. PK parameter values were more closely correlated with BSA than with BW. The inclusion of BSA decreased the inter-individual variability by 45%. The inclusion of BW0.78 decreased the inter-individual variability by 50% Conclusion: The results of our study confirmed large inter-individual variability for carboplatin in dogs and a larger improvement in the fit associated to BW0.78 than to BSA. The model obtained in this study should allow more accurate prediction of carboplatin clearance in dogs, and hence doses required to achieve target AUC values.

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“The Impact of Physical Inactivity on Breast and Colon Cancer Worldwide”

Dr. Gregory W. Heath
Guerry Professor and Assistant Vice Chancellor for Research
University of Tennessee at Chattanooga
Professor of Medicine and Research Director
University of Tennessee College of Medicine Chattanooga

Strong evidence shows that physical inactivity increases the risk of many adverse health conditions, including major non-communicable diseases such as breast and colon cancers, and shortens life expectancy. Because much of the w world’s population is inactive, this link presents a major public health issue. For our analysis of burden of disease, we calculated population attributable fractions (PAFs) associated with physical inactivity using conservative assumptions for breast cancer in women and colon cancer, by country, to estimate how much disease could be averted if physical inactivity were eliminated. Worldwide, we estimate that physical inactivity causes 10% of the burden of (range 5·6–14·1) breast cancer, and 10% (range 5·7–13·8) of colon cancer. Physical inactivity has a major health effect on these cancers worldwide. Decrease in or removal of this unhealthy behavior could improve global health substantially.

POSTERS

(1) "ORMELOXIFENE ATTENUATES WNT/β-CATENIN SIGNALING IN COLON CANCER CELLS BY MODULATION OF PKD1 AND GLYCOLYTIC PATHWAYS"

Aditya Ganju[1], Rishi Gara[1], Sonam Kumari[1], Man Mohan Singh[2], Subhash C. Chauhan[1], Meena Jaggi[1]

[1]University of Tennessee Health Science Center, Memphis, TN
[2]Saraswati Dental College, Lucknow, UP, India

Aberrant Wnt/β-catenin signaling is implicated in development and progression of colon cancers. Therefore, modulation of this master regulatory signaling is essential for the prevention and treatment of colon cancer. Protein Kinase D1 (PKD1) which is downregulated in colon cancer, regulates β-catenin transcriptional activity by its phosphorylation. Therefore, drug mediated upregulation of PKD1 may have high clinical significance for the prevention/treatment of Wnt/β-catenin signaling induced cancers. We have identified, ormeloxifene, a synthetic non-steroidal selective estrogen receptor modulator (SERM), as a novel PKD1 modulator. Herein, we have investigated the effect of ormeloxifene on tumorigenic phenotypes of colon cancer cells and its effect on PKD1 and glycolytic pathways mediated oncogenic β-catenin signaling. Ormeloxifene treatment restores PKD1 expression, thereby, attenuates β-catenin transcriptional activity. We have also observed that ormeloxifene treatment effectively inhibits CCL2 expression, glucose uptake, glucose metabolism and Glut1 receptor expression in cancer cells. Ormeloxifene (5-20μM) inhibits cell proliferation and motility of colon cancer cells. Additionally, ormeloxifene effectively inhibited CCL2 mediated cellular migration of colon cancer cells. Furthermore, Western blot results depict that PKD1 inhibits TCF4 activity in colon cancer cells. SW480 PKD1 overexpressing cells clearly delayed tumor formation in nude mice compared to control cells. In addition, SW480-PKD1-GFP cells showed less hypoxia (Glut1) and increased Vasculature (CD31) in tumors. Our findings demonstrate that ormeloxifene treatment effectively attenuates β-catenin mediated oncogenic signaling and tumorigenic phenotypes of colon cancer cells via upregulation of PKD1 and suppression of glycolytic pathways. Thus it can be used as a potential new preventive/treatment modality for colon cancer.

(2) "BICONTINUOUS MICROEMULSIONS AS A BIOMEMBRANE MIMETIC SYSTEM FOR MELITTIN"

Douglas G. Hayes[1], Ran Ye[1], Rachel N. Dunlap[2], Divina B. Anunciado[2], Sai Venkatesh Pingali[2], Hugh M. O'Neill[2], Volker S. Urban[2]

[1]University of Tennessee- Knoxville, Knoxville, TN
[2]Oak Ridge National Laboratory, Oak Ridge, TN

Antimicrobial peptides effectively kill antibiotic-resistant bacteria by forming pores in prokaryotes' biomembranes via penetration into the biomembranes' interior. Bicontinuous microemulsions, consisting of interdispersed oil and water nanochannels separated by flexible surfactant monolayers, are potentially valuable for membrane-associated peptides and proteins due to their thermodynamic stability, optical transparency, low viscosity, and high interfacial area. Here we show that bicontinuous microemulsions formed by negatively-charged surfactants are a robust biomembrane mimetic system for the antimicrobial peptide melittin. When encapsulated in bicontinuous microemulsion phase of three-phase (Winsor-III) systems, melittin exists in a highly folded state and penetrates into the surfactant monolayers, mimicking its behavior in biomembranes. But, the threshold melittin concentration required to achieve these trends is lower for the microemulsions. The extent of penetration was decreased when the interfacial fluidity of the microemulsions was increased. These results suggest the utility of bicontinuous microemulsions for isolation, purification, delivery, and host systems for antimicrobial peptides.

(3) "ORMELOXIFENE, A NOVEL PHARMACOLOGICAL ACTIVATOR OF PKD1 ENHANCES DOCETAXEL SENSITIVITY IN PROSTATE CANCER"

Aditya Ganju[1], Bilal Bin Hafeez[1], Fathi Halaweish[2], Wei Li[1], Man Mohan Singh[3], Subhash C. Chauhan[1], Meena Jaggi[1]

[1]University of Tennessee Health Science Center, Memphis, TN
[2]South Dakota State University, Brookings, South Dakota
[3]Saraswati Dental College, Lucknow, UP, India

Protein Kinase D1 (PKD1), one of the serine threonine kinases from PKD family is highly expressed in normal prostate tissues and is suppressed during Prostate Cancer (PrCa) progression. Accumulative evidence suggests a tumor suppressive role of PKD1 in PrCa, while other isoforms of PKD (PKD2 and PKD3) act as oncogene. Docetaxel (DTX) is a standard first-line treatment for metastatic castration-resistant PrCa after the failure of hormone therapy. However, most PrCa patients who receive DTX experience only transient benefits and rapidly develop incurable drug resistance. In this study, we identified pharmacological agent Ormeloxifene (ORM) which selectively activates PKD1 and inhibits metastasis associated protein 1 (MTA1), thus induces sensitivity to DTX treatment in PrCa cells. ORM treatment inhibits proliferation and clonogenic potential of C4-2 cells. We observed that ORM significantly induces PKD1 expression at protein and mRNA level in C4-2 cells. To determine whether this PKD1 inducing effects of ORM in PrCa cells is specific, we examined the effects of ORM on PKD2 and PKD3 at mRNA and protein levels. Interestingly, we observed that ORM treatment inhibits expression of oncogenic PKD3 isoform, however, no effect PKD2 was observed. MTA1 is involved in DTX resistance and ORM treatment effectively inhibited the expression of MTA1. However, there was no effect of DTX treatment on the expression of MTA1. We also observed that ORM treatment significantly potentiates the effect of DTX on cell viability and colony formation of C4-2 cells. In-silico docking studies between ORM and MTA1 showed four potential binding sites with best score at serine 270. Overall, our study defines ORM as a novel PKD1 activator/modulator which also inhibits a key metastasis associated protein, MTA1 and sensitizes the PrCa cells to DTX. Based on these results, it appears that ORM may be a novel therapeutic modality for advanced stage metastatic PrCa alone or in combination with DTX.

(4) "COMORBIDITY FACTORS ASSOCIATED WITH HUMAN PAPILLOMAVIRUS INFECTIVITY: IMPLICATIONS IN CERVICAL CANCER HEALTH DISPARITY"

Vivek K. Kashyap[1], Sheema Khan[1], Mohammad Sikander[1], Diane M. Maher[2], Santosh Kumar[1], Namita Sinha[1], Murali M. Yallapu[1], Nadeem Zafar[1], Meena Jaggi[1], Subhash C. Chauhan[1]

[1]University of Tennessee Health Science Center, Memphis, TN
[2]Sanford Research, Sioux Falls, SD

Objective: High -risk strains of human papillomavirus (HPV), HPV E6/E7 cause cervical cancer (CxCa). Certain underserved populations in the United States, such as American Indian and 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 factors, namely, smoking, alcohol and HIV coinfection on the HPV infectivity. Method: Caski and SiHa cells were treated with a smoking carcinogens Benzo[a]Pyrene (BaP) or alcohol (EthOH) or both. Effects of this treatment was analyzed on cell proliferation, clonogenicity, cell migration, cell cycle and the expression of HPV E6/E7 was determined by qRTPCR, immunoblotting and confocal microscopy. The effect of HIV coinfection on the expression of HPV E6/E7 was also investigated by incubating CxCa cells with conditioned medium derived from HIV infected U937 monocytic cells (U1). Result: Our results show that the exposure of BaP or EthOH or their combination enhances the expression of HPV E6/E7oncogenes. Additionally, cells treated with BaP and EthOH alone or in combination show higher

oncogenic phenotypes as evident by increased cell proliferation, clonogenicity and cell migration and invasion. These cofactors in presence of HIV coinfection also augment the expression of HPVE6/E7 oncogenes. Interestingly, curcumin and its nanoparticle formulation (NanoCur) effectively inhibit BaP/EthOH induced expression of E6/E7 oncogenes, growth, and migration of CxCa cells and induces apoptosis. 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/nanocurcumin treatment. This provides hope for developing a feasible approach to reduce CxCa health disparity among underserved populations.

(5) "MUC13 INTERACTION WITH RECEPTOR TYROSINE KINASE HER2 DRIVES PANCREATIC DUCTAL ADENOCARCINOMA PROGRESSION"

Sheema Khan, Mohammad Sikander, Aditya Ganju, Bilal B. Hafeez, Sonam Kumari, Murali M. Yallapu, Stephen Behrman, Nadeem Zafar, Meena Jaggi, Subhash C. Chauhan

University of Tennessee Health Science Center, Memphis, TN

Pancreatic Ductal Adenocarcinoma (PDAC) is the fourth leading cause of cancer related death in the United States and has a very poor survival rate due to late diagnosis. MUC13 is a recently identified high molecular weight glycoprotein that is upregulated in PDAC and its progression is allowed via alterations of multiple signaling pathways. MUC13 correlates with increased expression of HER2, however, the underlying mechanism remains poorly understood. MUC13 consists of three EGF-like domains that may serve as a ligand for EGF receptors, such as HER2, and modulate EGFR signaling pathways. We sought to better characterize the interaction of MUC13 with HER2 MUC13 colocalizes and interacts with HER2 in PDAC cell lines. The results from this study demonstrate that MUC13 functionally interacts and activates HER2 in PDAC cells, leading to stimulation of HER2 signaling cascade including, ERK1/2, FAK, AKT and PAK1 as well as regulation of the growth, cytoskeleton remodeling, motility and invasion of PDAC cells all collectively contributing to PDAC progression. The interaction between MUC13-HER2 binding resulting in their tumorigenic characteristics likely occurs at the 1st and 2nd domains of MUC13 as the EGF 1 and 2 deletion mutant constructs of MUC13 failed to promote proliferation and invasion of cells. These phenotypic effects of MUC13 HER2 colocalization could be effectively compromised by depleting MUC13. MUC13-HER2 colocalization also held true in PDAC human tissues with a strong functional correlation that contributed to an increased degree of disorder and cancer aggressiveness. In conclusion, findings presented here provide compelling evidence of a functional ramification of MUC13-HER2: this interaction could be potentially exploited for targeted therapeutics in a subset of patients harboring an aggressive form of PDAC.

(6) "ROLE OF MUC13 AS NON-HYPOXIC STIMULI INDUCING HIF-1α IN PANCREATIC CANCER UNDER NORMOXIA"

Sonam Kumari, Sheema Khan, Murali M. Yallapu, Meena Jaggi

University of Tennessee Health Science Center, Memphis, TN

Background: Pancreatic cancer is the fourth most common cause of deaths occurring due to cancer, with an overall survival rate of just 5%. MUC13, a transmembrane mucin, is aberrantly expressed in pancreatic cancer, while an altered glucose metabolism is known to facilitate cancer cell survival and proliferation. Hypoxia-inducible factor 1 (HIF-1 α) plays an important role in reprogramming of cancer cell metabolism by activating the transcription of genes which encode glucose transporters and enzymes involved in glycolysis. Recent reports suggest that several non-hypoxic stimuli such as lipopolysaccharides, thrombin, and angiotensin II can also increase HIF-1α levels under normoxia. Herein, we investigated the effects of MUC13 expression on glucose metabolism and elucidated underlying signaling mechanisms that might be involved in this process. Results: Our results

demonstrate that MUC13 acts as a modulator of the glucose metabolism in pancreatic cancer cells by regulating the expression and activity of hypoxia-inducible factor-1α (HIF-1α) and its downstream targets. We observed increased amount of L-lactate production and glucose consumption in Panc-1-M13 cells as compared to Panc-1-V cells. This facilitates metabolic alterations and help tumor cells survive and proliferate under these conditions as indicated by increase cellular growth pattern in Panc-1-M13 cells. Our results demonstrate increased expression of the downstream targets of HIF-1α, such as cell regulatory (c-Myc), and cell survival (Bcl-2) proteins, while decreased the expression of tumor suppressor/cell cycle inhibitor (p-27) proteins in Panc-1-M13 cells. Also, an increase in the expression of a critical downstream target of HIF-1α, Glut-1 was observed in Panc-1-M13 cells. Conclusion: Our studies show that MUC13 acts as a key regulator of the metabolic process and facilitates metabolic alterations in the non-hypoxic environment that help tumor cells proliferate under these conditions.

(7) "DISCOVERY OF ABI-231 ANALOGS AS A NEW GENERATION OF TUBULIN INHIBITORS TARGETING THE COLCHICINE BINDING SITE"

Qinghui Wang, Kinsie Arnst, Duane D Miller, Wei Li

University of Tennessee Health Science Center, Memphis, TN

Despite recent advances in both targeted therapy and immunotherapy, acquired drug resistance often develops quickly and the overall survival for malignant cancers including melanoma remains unsatisfactory. Our ongoing research in developing new generations of tubulin inhibitors have resulted in several sets of unique structures from our initial thiazole analog that: 1) target the colchicine binding site in tubulin and have broad spectrum of potent anticancer activity; 2) effectively circumvent major drug resistance mechanisms that hinder the clinical efficacy with existing tubulin inhibitors; 3) are orally bioavailable and have excellent drug-like properties; and 4) are efficacious against both drug sensitive and drug resistant melanoma tumors in vivo, with ABI-231 as the best lead compound. Further structure optimization provided more than 40 new analogs, with 6ab being the most potent analog, with GI50 values approaching pM range in some cell lines based on our in-house assays and the NCI-60 cell line assays. Mechanistic studies indicated that these compounds effectively inhibit tubulin polymerization, strongly induce cancer cell apoptosis and cancer cell colony formation, arrest cancer cells in G2/M phase, have minimal potential off-target effects as demonstrated by the SafeScreen44 assay, and potently inhibit melanoma tumor growth in vivo. We have also successfully obtained very high resolution X-ray crystal structures (2.2 to 2.5 Å) for the most active compounds in complex with tubulin, further confirmed their molecular interactions with tubulin and their mechanism of actions. These compounds represent a unique scaffold as orally bioavailable tubulin inhibitors, and are currently being developed for future clinical application for a variety of cancer types.

(8) "THERAPEUTIC POTENTIAL OF BROMO-ORMELOXIFENE IN CERVICAL CANCER"

Shabnam Malik[1], Mohammed Sikander[1], Bilal Bin Hafeez[1], Aditya Ganju[1], Fathi T. Halaweish[2], Subhash C. Chauhan[1], Meena Jaggi[1]

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Cervical cancer is one of the most common cancer in women worldwide and is fully associated with persistent of Human papilloma virus (HPV) infection. E6 and E7 oncoproteins of HPV are well known to interfere with retinoblastoma (Rb) protein and leads to the development of cervical cancer. Ormeloxifene is a non-steroidal drug that has a well-defined pharmacokinetic (PK) and pharmacodynamic (PD) profile in human applications. Ormeloxifene (ORM) is a non-hormonal oral contraceptive molecule that has potent anti-cancer properties. We have synthesized novel analogues of ormeloxifene which showed an enhanced therapeutic efficacy as compared to parent compound ormeloxifene. We have investigated the antiproliferative activity of this analogue in cervical cancer

(CaSki and SiHa) cells. MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) and colony formation assays were performed to investigate anti-cancer effects of Br-ORM. Br-ORM treatment inhibited cell proliferation in dose and time dependent manner. Br-ORM treatment also induced apoptosis as studied by enhanced Annexin V detection kit and increase in PARP cleavage as seen by Western blotting. In addition, migration abilities were also reduced as studied by agarose bead and wound healing assays. Flow cytometry analysis showed cell cycle arrest in G1-S phase transition. Further, Br-ORM treatment decreased the phosphorylation of retinoblastoma protein and cyclin dependent kinase 4 expression level. In addition, drug treatment modulates the expression of key oncogenic effectors including PI3K, AKT and β-catenin. Interestingly, Br-ORM restores the expression of tumor suppressor miR-200a as studied by qRT-PCR. Taken together, our results demonstrate potent anti-cancer efficacy of Br-ORM in cervical cancer.

(9) "DEVELOPMENT OF NEW THERAPEUTIC APPROACHES FOR PANCREATIC CANCER TREATMENT"

Subhash C. Chauhan[1], Murali M. Yallapu[1], Sheema Khan, Mara C. Ebeling[2], Meena Jaggi[1], Satoshi Nagata[3], Stephen W. Behrman[1], Nadeem Zafar[1], Jim Y. Wan[1], Prabhakar Pradhan[4]

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Pancreatic cancer (PanCa), is the fourth leading cause of cancer related deaths in the United States due to the lack of early diagnosis and poor response to available therapeutics. Thus, identification of newer therapeutic approaches that can aid current therapeutics is highly desirable. We have defined multidimensional roles of MUC13 mucin in the pathogenesis and therapeutics/imaging of PanCa. We have reported that MUC13 is highly expressed in human pancreatic tumors but not in normal pancreas and its expression progressively increases with disease stage and metastasis. MUC13 enhances tumorigenesis through modulation of multiple oncogenes (HER2, PAK1, ERK, metastasin/S100A4, TERT, sonic hedgehog (SHH), GATA-1) associated with tumorigenesis/metastasis and desmoplasia. Additionally, we have identified drugs that inhibit tumor desmoplasia (targets SHH pathway) and enhances therapeutic response of gemcitabine, thus, can be of therapeutic benefit for PanCa. Moreover, we have generated unique anti-MUC13 mouse monoclonal (MAb) and recombinant humanized (HuAb) antibodies that can efficiently target pancreatic tumors. Furthermore, we have successfully generated multiple patented nanoparticle formulations for antibody guided tumor specific targeted drug delivery and imaging. Taken together, our data suggest a crucial role of MUC13 in PanCa pathogenesis. Utilization of a novel anti-MUC13 monoclonal antibody can be used for the targeted tumor specific delivery of novel nanoparticle formulations in pancreatic tumors. This research will establish the multifaceted role of MUC13 in pathogenesis of PanCa and advance diagnosis and therapy of PanCa.

(10) "MIRNA203 SUPPRESSES THE EXPRESSION OF PROTUMORIGENIC STAT1 IN GLIOBLASTOMA TO INHIBIT TUMORIGENESIS"

Chuan He Yang, Yinan Wang, Michelle Sims, Chun Cai, Ping He, Junming Yue, Jinjun Cheng, Frederick A. Boop, Susan R. Pfeffer, Lawrence M. Pfeffer

University of Tennessee Health Science Center, Memphis, TN

MicroRNAs (miRNAs) play critical roles in regulating cancer cell proliferation, migration, survival and sensitivity to chemotherapy. The potential application of using miRNAs for cancer prognosis holds great promise but miRNAs with predictive value remain to be identified and underlying mechanisms

of how they promote or suppress tumorigenesis are not completely understood. Here, we show a strong correlation between miR203 expression and brain cancer patient survival. Low miR203 expression is found in subsets of brain cancer patients, especially glioblastoma. Ectopic miR203 expression in glioblastoma cell lines inhibited cell proliferation and migration, increased sensitivity to apoptosis induced by interferon or temozolomide in vitro, and inhibited tumorigenesis in vivo. We further show that STAT1 is a direct functional target of miR203, and miR203 level is negatively correlated with STAT1 expression in brain cancer patients. Knockdown of STAT1 expression mimicked the effect of overexpression of miR203 in glioblastoma cell lines, and inhibited cell proliferation and migration, increased sensitivity to apoptosis induced by IFN or temozolomide in vitro, and inhibited glioblastoma tumorigenesis in vivo. High STAT1 expression significantly correlated with poor survival in brain cancer patients. Mechanistically, we found that enforced miR203 expression in glioblastoma suppressed STAT1 expression directly, as well as that of a number of STAT1 regulated genes. Taken together, our data suggest that miR203 acts as a tumor suppressor in glioblastoma by suppressing the pro-tumorigenic action of STAT1. MiR203 may serve as a predictive biomarker and potential therapeutic target in subsets of cancer patients with low miR203 expression.

(11) "A PROBABILISTIC GENE NETWORK MODEL AND ITS APPLICATIONS ON AGING AND CANCER"

Hong Qin

University of Tennessee-Chattanooga, Chattanooga, TN

Why would a genotypically homogeneous population of cells live to different ages? We propose a mathematical model of cellular aging based on gene interaction network. This model network is made of only non-aging components, and interactions among genes are inherently stochastic. Death of a cell occurs in the model when an essential gene loses all of its interactions. The key characteristic of aging, the exponential increase of mortality rate over time, can arise from this model network with non-aging components. Hence, cellular aging is an emergent property of this model network. The model predicts that the rate of aging, defined by the Gompertz coefficient, is proportional to the number of active interactions per gene and that stochastic heterogeneity is an important factor in shaping the dynamics of the aging process. Hence, the Gompertz parameter is a proxy of network robustness. Preliminary studies on how aging is influenced by power-law configuration, synthetic lethal interaction, and allelic interactions can be modeled. A general framework to study network aging as a quantitative trait has also been found, and the results has implication on missing heritability. Preprint for the basic model is available at http://arxiv.org/abs/1305.5784. Moreover, we are developing similar probabilistic gene network models for cancer cells.

(12) "CD-19-TARGETED CYTOTOXIC T CELLS FOR LUPUS THERAPY"

Marko Radic

University of Tennessee Health Science Center, Memphis, TN

Lupus is an autoimmune disease with multifactorial modes of presentation that can progress to serious and sometimes lethal outcome. Progress in developing effective and targeted treatments has been slow and disappointing. One generally accepted feature of immune disturbance in lupus is the production of diverse autoantibodies that are diagnostic and possibly pathogenic due of their ability to form immune complexes. To develop a new experimental therapy for lupus, we adopted a technology that has shown promise in the field of cancer immunotherapy. In B cell leukemia, exciting progress has been made in using autologous (patient-derived) cytotoxic T cells (CD8+ T cells) for the purpose of eliminating the cancerous B cells. The CD8+ T cells are isolated from the patient and programmed with the capacity to recognize and lyse cancer cells. Such engineered T cells express so-called chimeric antigen receptors (CARs). We have used CAR T cells to deplete B cells in a mouse

model of lupus (NZBxNZW F1 female mice). We find that mice that receive anti-CD19 T cells show a reduction of B cell numbers that is long-lasting and can extend the life span in this autoimmune model to beyond 1 year of age. Long-term surviving mice show a decrease in circulating antibody levels and anti-DNA autoantibodies. Moreover, such mice show reduced immune complex deposition in kidneys. We identify a T cell population that persists in these mice, exhibits effector memory phenotype and continually expresses the CAR construct. We plan to use the CAR approach to evaluate the effectiveness of this technology to prevent or reverse the disease course in NZBxNZW F1 female mice. Long-term goals that will be pursued are the design and testing of B cell subtype-specific CARs that could allow a large part of the humoral immune system to remain intact.

(13) "PRE-CLINICAL IN VIVO BIOLUMINESCENT/FLUORESCENT IMAGING CORE RESEARCH FACILITY"

Steven Ripp, Tingting Xu

University of Tennessee-Knoxville, Knoxville, TN

The Bioimaging Core at the University of Tennessee – Knoxville provides cutting-edge bioluminescent and fluorescent biological imaging to the UT-Knoxville and surrounding research community. Our primary bioimaging instrumentation consists of two in vitro/in vivo/ex vivo/in planta PerkinElmer IVIS Lumina imaging systems that enable visualization of light emission from fluorescent and bioluminescent proteins, dyes, and nanomaterials directly within living animals, tissues, cells, whole plants, and biomaterials. For cancer research in particular, these imaging systems are supporting a number of research projects that involve the in vivo visualization of tumor growth, monitoring drug delivery, tracking cell migration dynamics, assessing the biocompatibility of three-dimensional tissue scaffolds, and brain imaging. Our newest IVIS Lumina K instrument provides fast frame capture to enable animals to be imaged as they freely move about their enclosure without anesthetization. Staff is available to provide individual to classroom-level instrument training and assistance with data analysis to ensure that you and your lab's investigational and developmental needs are optimally met, and we are always open to productive collaborations with academic institutions outside of the Knoxville area.

(14) "IDENTIFICATION OF NOVEL HIF-DEPENDENT TARGET GENES IN A MOUSE MODEL OF METASTATIC BREAST CANCER"

Danielle L. Peacock, Luciana P. Schwab, Keisha D. Smith, Richard C. Cushing, Tiffany N. Seagroves

University of Tennessee Health Science Center, Memphis, TN

Hypoxia is a hallmark of most solid tumors. Under hypoxic stress tumor cells adapt by regulating survival, metabolism and angiogenesis. The heterodimeric Hypoxia-Inducible Factor (HIF)-1 transcription factor is a master regulator of this response, and is comprised of HIF-1α, the oxygen-regulated subunit, and aryl hydrocarbon nuclear receptor translocator (ARNT), which is constitutively expressed. HIF-1α protein is over-expressed in ~30% of primary breast tumors and ~70% of metastases. Over-expression of HIF-1α is independently correlated with poor prognosis and decreased survival in breast cancer patients. In agreement with these observations, conditional deletion of HIF-1 represses tumor initiation and lung metastasis in the MMTV-polyoma virus middle T (MMTV-PyMT) model of breast cancer. Primary mammary tumor epithelial cells (MTECs) were established from late stage carcinomas originating in PyMT+; Hif1a floxed mice maintained on an inbred background (FVB/Nj). MTECs were exposed ex vivo to Adenovirus-β-gal or -Cre to create wild type (WT) and knockout (KO) cells, respectively; cells were then re-introduced into the mammary fat pad of FVB/Nj recipients. HIF-1α deletion reduced primary tumor growth by ~60% and lung macrometastases by ~90%. To identify HIF-dependent target genes, microarray profiling was

performed. Several genes were differentially expressed between both WT and KO cells cultured at normoxia (21% O2) or hypoxia (0.5% O2) and end-stage WT and KO tumors. Of particular interest, creatine kinase, brain isoform (CKB) mRNA levels were reduced >100-fold in KO cells and >2-fold in KO end-stage tumors. Two independent shRNA constructs (shc59 and shc61) were generated to stably knockdown CKB in WT PyMT cells to assay for effects on invasion and metastasis. Loss of CKB function potently reduced invasion in vitro and reduced primary tumor growth and lung metastasis in vivo, suggesting that targeting CKB may be a novel intervention for metastatic breast cancer.

(15) "RESTORATION OF MICRORNA-145 USING MAGNETIC NANOFORMULATION INHIBITS PANCREATIC CANCER"

Saini Setua, Sheema Khan, Murali M. Yallapu, Mohammed Sikander, Stephen W. Behrman, Meena Jaggi, Subhash C. Chauhan

University of Tennessee Health Science Center, Memphis, TN

Background: Pancreatic cancer (PanCa) is the fourth leading cause of cancer related deaths in the USA. MicroRNAs have been identified as attractive targets for therapeutic intervention. The functional significance of lost microRNAs are reported in several human malignancies, including pancreatic cancer. Therefore, restoring lost miRNA function can provide a therapeutic benefit. Recently, we have identified microRNA-145 (miR-145) as a novel tumor suppressor miRNA in pancreatic cancer and restoration of miR-145 efficiently inhibited tumor growth in mice. The main challenge for successful translation of microRNAs into the clinic remains *in vivo* delivery, therefore, the focus of this study is to develop a novel miRNA delivery method for therapeutic purposes.
Results: miR-145 expression was progressively suppressed over the course of development from PanIN I-III to late stage poorly differentiated PDAC. We have developed a magnetic nanoparticle (MNP) based nanoformulation of miR-145 (miR-145-MNPF) for the intracellular delivery and sustained release of miR-145. We have used positively charged polyethyleneimine molecules to increase the loading efficiency of miR-145. MUC13 expressing pancreatic ductal adenocarcinoma cell lines (HPAF-II and AsPC-1) were used for the study. Treatment of cells with miR-145-MNPF led to efficient intracellular delivery of miR-145 mimics as observed through prussian blue staining and simultaneous upregulation of miR-145 levels in cells as confirmed by qRT-PCR. miR-145 restitution resulted in significant downregulation of target oncogenes including MUC13, HER2, P-AKT and p53 as observed through Western blotting. miR-145-MNPF inhibited cell proliferation, clonogenicity, migration, and invasion of PC cells.
Conclusions: 1) MNP based delivery systems can be efficiently used for microRNA replacement therapy in order to restore lost microRNAs in cancer. 2) miR-145-MNPF efficiently restores miR-145 in pancreatic cancer cells and inhibits growth and invasion of PanCa. 3) miR-145 restitution using miR-145-MNPF may offer a potential therapeutic strategy for pancreatic cancer treatment alone or in combination with other therapies.

(16) "CUC D: A NOVEL ANALOGUE OF CUCURBITACIN INHIBITS CERVICAL CANCER CELL GROWTH IN IN VITRO AND XENOGRAFT MOUSE MODEL"

Mohammed Sikander[1], Bilal Bin Hafeez[1], Shabnam Malik[1], Fathi T. Halaweish[2], Murali M. Yallapu[1], Meena Jaggi[1], Subhash C. Chauhan[1]

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Cervical cancer is one of the leading causes of mortality among women in US. Naturally occurring dietary compounds have gained increasing attention for their anticancer efficacy. Cucurbitacins, tetracyclic triterpenoid compound, belong to a family of Cucurbitaceae have shown promising

anti¬cancer activity. Herein, we investigated the potential anti¬cancer effects of a novel analogue of cucurbitacin D (Cuc D) against cervical cancer in in vitro and in a xenograft mouse model. In our study, we used human cervical cancer cells (CaSki and SiHa). Cells were treated with Cuc D (0.05 to 1μM) for 48 and 72 hrs. MTS and colony formation assays were performed to investigate the effects of Cuc D on cell viability and proliferation. Western Blot analysis was performed to investigate the effects of Cuc D on cell proliferation and apoptotic markers. To determine the therapeutic effects of Cuc D, we used female athymic nude mice and injected CaSki cells (4 x 106) into the cervix to develop orthotopic xenograft tumors. Cuc D (1 mg/kg body weight) was administered through intra-tumoral injection four weeks post-¬tumor cell injection. Tumor volume in these mice were recorded bi¬weekly. Cuc D inhibited cell viability of cervical cancer cells in a dose ¬dependent manner. IC50 of Cuc D was observed 400 nM and 250 nM in Caski and SiHa cells, respectively. Cuc D treatment effectively inhibited growth of cervical cancer cells which was determined by decreased cell proliferation and colony formation assays. Cuc D treatment induced apoptosis in cervical cancer cells as measured by enhanced Annexin V staining. Western blot result also illustrated cleavage in PARP protein in Cuc D treated cells which further confirms apoptosis induction. Cuc D treatment also inhibited PI3K and c¬-Myc protein levels and phosphorylation of STAT3 and Rb proteins.

(17) "DNA DAMAGE-INDUCED NF-KB ACTIVATION PROMOTES BREAST CANCER METASTASIS VIA UPREGULATION OF MICRORNA-21"

Jixiao Niu, Guangyun Tan, Chuan He Yang, Meiyun Fan, Lawrence Pfeffer, Zhaohui Wu

University of Tennessee Health Science Center, Memphis, TN

Nuclear Factor kappaB (NF-kB) activation induced by genotoxic treatment in cancer cells has been associated with therapeutic resistance in multiple human malignancies. Therapeutic resistance also correlates with high metastatic potential in human cancers including breast cancer. Whether genotoxic treatment-activated NF-kB also contributes to cancer metastasis following radiation and chemotherapy is unclear. Here we show that chemotherapeutic drug-induced NF-kB activation promotes breast cancer cell migration and invasion. The increased metastatic potential is dependent on IL-6 induction mediated by genotoxic NF-kB activation. Moreover, genotoxic treatment also upregulates oncogenic microRNA-21 expression through eliciting NF-kB recruitment to miR-21 promoter region, where it cooperates with signal transducer and activator of transcription 3 (STAT3) to activate miR-21 transcription. NF-kB-dependent IL-6 upregulation is responsible for STAT3 activation and recruitment to miR-21 promoter upon genotoxic stress. Induction of miR-21 may enable cancer cells to elude DNA damage-induced apoptosis and enhance the metastatic potential of breast cancer cells through repressing expression of PTEN and PDCD4. Our data support a critical role of DNA damage-induced NF-kB activation in promoting cancer metastasis following genotoxic treatment, and NF-kB-dependent miR-21 induction may contribute to both therapeutic resistance and metastasis in breast cancer.

(18) "PACLITAXEL SELF-ASSEMBLIES FOR BREAST CANCER THERAPY"

Pallabita Chowdhury, Prashanth K.B. Nagesh, Sheema Khan, Subhash C. Chauhan, Meena Jaggi, Murali M. Yallapu

University of Tennessee Health Science Center, Memphis, TN

Breast cancer (BC) is second greatest cause of cancer-related death 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 chemoresistance against it, limits its use in the clinic. Minimizing the toxicity issues of Ptx through nanoparticle technology is feasible and has displayed encouraging outcomes. With this background, we aim to generate Ptx self-assemblies (PSAs) using various biocompatible polymers and surfactants, and to evaluate its efficacy against BC

cells. PSAs 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 PSAs. The optimal polymers for forming PSAs were identified through measurement of particle size, zeta potential and TEM. Another check point of generating a better PSAs was evaluated by its extent of cellular internalization in BC cells and through hemolytic assay. Finally, the finalized PSAs were examined for in vitro activity in BC cells using proliferation, colony formation, and immunoblotting assays. We screened 22 biocompatible polymers for PSA 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 PSAs exhibited enhanced anti-cancer capability in MCF-7 and MDA-MB-231 BC cells in proliferation and colony formation assays, compared to free Ptx. Further, PSA treatment in BC cells demonstrates a superior induction of the expression of apoptosis-associated proteins and downregulation of anti-apoptotic proteins. Overall this study suggests a simple and feasible Ptxl self-assembly approach for achieving superior anti-cancer activity with Ptx.

(19) "SALIVA METABOLOMICS"

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Objectives: To study the saliva metabolomics among subjects treated with Listerine®. Methods: 23 adult subjects were enrolled (UTHSC IRB # 14-03047-XP). Subjects visited the clinic before oral hygiene/breakfast, a baseline saline rinse and whole saliva samples were collected. Subject then rinsed his/her mouth with 20 mL of Listerine for 30 seconds and spit it out, 45 minutes post treatment, saline rinse and whole saliva samples were collected again. Samples were aliquoted and stored at -75°C. For NMR analysis, samples were thawed out and clarified by centrifugation at 3000 g for 10 minutes, the supernatant was lyophilized overnight and dissolved in D2O. 1D Proton NMR data were collected using a Bruker AVANCEIII 400MHz NMR spectrometer (Bruker BioSpin Co., Billerica, MA). Chemical shifts were referenced according to the H2O peak at 4.76ppm. Metabolites were identified using MetaboHunter (Tulpan D, 2011). Results: 23 Metabolites were identified: Oxalacetic acid; Dimethylmalonic acid; 9-Methyluric acid; 1,3,7-Trimethyluric acid; 3,7-Dimethyluric acid; Guanidoacetic acid; 2,5-Furandicarboxylic acid; Hydroquinone; 2-Aminoisobutyric acid; 3-Hydroxyisovaleric acid; Pyruvic acid; Phosphoenolpyruvic acid; Dimethylsulfide; Acetoacetic acid; Quinone; Guanine; Dimethylamine; 2,4-Diamino-6-hydroxypyrimidine; Urea; Glycine; Glycolic acid; D-Threitol; Choline. Among them, Oxalacetic acid, Dimethylmalonic acid and 9-Methyluric acid were found in all the four types of samples. Conclusion: To date, 1D Proton NMR data were acquired from 40 saline rinse and whole saliva samples, 23 metabolites were identified for comparison. Keywords: Saliva, metabolomics, NMR, Listerine, clinical trial Acknowledgements: Supported in part by the UTHSC College of Dentistry Alumni Endowment Fund and the Tennessee Dental Association Foundation

(20) "A REVIEW OF CLINICAL PHARMACIST IMPACT IN OUTPATIENT ONCOLOGY PRACTICES"

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Background: The incorporation of clinical pharmacists into outpatient oncology clinics has risen in recent years in the US; however, the evidence base behind the services provided has not been well articulated. This review summarized evidence from published literature detailing the impact of clinical pharmacists in outpatient clinics on discrete outcomes. Methods: Peer-reviewed, published literature

evaluating services provided by clinical pharmacists in outpatient oncology clinics in the US was reviewed according to a study-specific protocol. To be considered, each publication must have indicated the evaluation of measurable services and outcomes focused on the care of oncology patients. Data from eligible studies from 1970-2016 (January) were extracted using a standardized tool and agreement by a majority of the authors was required for a publication to be included. Results: Eight publications were included; all studies were observational and employed either existing data, accessible medical records, or surveys. Results indicated that pharmacists were effective in several areas of clinical interest: identifying treatment issues or medication misuse; delivering satisfactory and valued services according to patients and providers; and addressing and alleviating treatment-related symptoms, particularly pain. Additionally, oncological pharmacists identified up $210,000 in avoidable services and were able to generate upwards of $840,000 in departmental revenue to justify services. Conclusions: While the prevalence of clinical pharmacists providing direct patient care in outpatient oncological practices is growing across the country, the peer-reviewed evidence base demonstrating their impact is lacking and deserves further inquiry through larger more robust analyses. The evidence reviewed suggests that oncology practices may benefit from leveraging clinical pharmacy services in their care model to more efficiently and holistically address patients' needs.

(21) “IDENTIFICATION OF IRON IN CELLS BY MÖSSBAUER SPECTROSCOPY”

Hien-Yoong Hah, Charles Johnson, Jacqueline Johnson, Julie King, Julie King, Sharon Gray

University of Tennessee Space Institute, Tullahoma, TN

Nanoparticles magnetic iron oxides have applications in medicine for targeting and destroying tumors and enhancing MRI images. These particles can be identified with Mössbauer Spectroscopy after injection into a cell. It is possible to distinguish these particles from other iron compounds in the human body, such as ferritin. Mössbauer Spectroscopy is a highly sensitive technique that probes the different nuclear transitions of the atoms, allowing differentiation of iron valencies. Furthermore, the magnetism of the compounds can be studied with the application of magnetic fields. At UTSI permanent magnets up to 2 T can be applied to magnetize and probe the compounds. In particular for single-domain iron oxide nanoparticles that are superparamagnetic, the magnetic susceptibility is greatly increased by the number of magnetic atoms in the particles (typically 104), and sizeable magnetizations may be produced at room temperature in fields of only 2 T.

(22) “NOMOGRAMS AND BIG DATA: PERFECT EMPIRICAL MATCH”

R. Eric Heidel

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Big data continues to make headlines in the empirical and data analytical fields. Big data allows for population-level inferences to be made regarding patient outcomes. Regression models can be greatly improved in terms of precision and accuracy when many observations are available for analysis. Further, nomograms, which are derived from regression models, provide cheap and easy methods for establishing the probability of events or diagnoses occurring in patient populations. With such large databases as the SEER and NCDB available, cancer researchers are uniquely positioned to excel with the creation of nomograms and analysis of population-level data.

(23) "UPREGULATION OF ATX EXPRESSION ARE UNIQUE FEATURES OF HIGHLY INVASIVE AND THERAPY-RESISTANT CANCER CELLS"

Sue Chin Lee[1], Raphael Leblanc[2], Derek D Norman[1], Yuko Fujiwara[1], Jianxiong Liu[1], Junming Yue[1], Souvik Banerjee[1], Duane D. Miller[1], Olivier Peyruchaud[2], Gabor J. Tigyi[1]

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Autotaxin (ATX) and lysophospholipid (LPA) represent two key players in regulating cancer progression. ATX is the primary enzyme involved in the production of LPA. Many of the biological functions of LPA are mediated by its actions on specific G protein-coupled LPA receptors (LPAR). In our studies, we have successfully established that silencing ATX expression in the murine B16F10 melanoma cells greatly reduced the number of lung metastasis in mice. Similar results were also obtained when ATX was inhibited using a pharmacological inhibitor. Apart from promoting metastasis, we also show that ATX and LPA2 receptor were found to be upregulated upon chemotherapy and radiation in murine 4T1 breast cancer stem-like cells (CSC). This is consistent with clinical data where ATX becomes overexpressed in patients with recurrent disease after prior chemotherapy. Thus, it appears that the upregulation of ATX expression, hence an increase in LPA production are central and unique features of highly invasive and therapy-resistant cancer cells.

(24) "3D GENOME STRUCTURE CHANGES DURING CANCER CELL MIGRATION"

Rosela Golloshi, Darrian Nash, Jacob Sanders, Peyton Terry, Rachel Patton McCord

University of Tennessee-Knoxville, Knoxville, TN

Metastasis, the most deadly part of cancer, results from cancer cell migration and invasion from a tumor into surrounding tissues. During this migration, the cell often has to squeeze and deform its nucleus through tight spaces. This nuclear squeezing is a rate-limiting step in migration, and the deformations can even rupture the nucleus. The organization of the genome inside the nucleus into loops, domains, and territories is important for proper gene regulation, DNA replication, and genome repair. However, little is known about the characteristics of nuclear organization that might allow for the nuclear deformation of metastatic cancer cells. We are using Chromatin Conformation Capture (Hi-C) and microscopy techniques to study genome organization during cancer cell migration. Using photoconvertible fluorophore Dendra2-H4 we can draw and monitor patterns on nuclei. Our preliminary data shows changes in these patterns, indicating spatial reorganization of the genome during migration. Previous work has suggested that cancer cell migration requires global condensation of the genome. Some cancer chemotherapeutics act on epigenetic marks to decondense chromatin. We hypothesize that this chromatin decondensation prevents the nucleus from deforming enough to migrate effectively. We have used transwell and wound healing migration assays to monitor migration of cells treated with epigenetically active cancer drugs. Our preliminary data shows that the drugs inhibit migration in a transwell assay but not in the wound healing assay. This suggests that genome decondensation prevents the passage of the nucleus through narrow 3D spaces. But, a condensed genome organization is not necessary for 2D cell motility, where nuclei are unconfined. In the future, we will perform Hi-C on cells squeezing through dense collagen matrices, which mimics the in vivo extracellular matrix. This will allow us to identify specific rearrangements in genome structure during cancer cell migration.

(25) "BIOSENSING INSTRUMENTATION AND DEVICES"

Nicole McFarlane

University of Tennessee-Knoxville, Knoxville, TN

We report on our progress for cell based, non-invasive, real time sensors. The sensors are based on low power electronics and offer low cost, accurate sensing. The devices are based on nano-fabrication and commercial complementary metal oxide semiconductor (CMOS) technology. We offer 1. impedance sensing for monitoring cell viability in real time, 2. optical sensing for imaging and detection, 3. bio-chemical analyte sensing (e.g. glucose), and 3. pH detection for chemical analysis.

(26) "CHANGING THE QUANTITATIVE PARADIGM IN PET/CT"

Dustin Osborne, Shelley Acuff

University of Tennessee Graduate School of Medicine, Knoxville, TN

Since its inception, the primary unit used in PET imaging has been the standard uptake value (SUV). The units normalize decay corrected counts from the scanner by the patient body weight and dose. Although useful, this unit is only semi-quantitative and is limited in its use as a comparative measure of patient disease response. It is possible to derive quantitative units from PET images but this process requires log dynamic acquisitions that can last more than an hour. These long scan times and the additional necessity to collect blood samples limits the use of these techniques in a typical clinical environment. This poster shows our groups efforts over the last few years developing and testing novel methods for acquiring whole body dynamic PET data within typical clinical scan times. We show a novel technique that is capable of acquiring whole body dynamic data within a 20-minute scan time. We also show how these data can be used to obtain true values for the patient's rate of glucose metabolism.

(27) "CHRONIC ETHANOL FEEDING PROMOTES AZOXYMETHANE AND DEXTRAN SODIUM SULFATE-INDUCED COLONIC TUMORIGENESIS BY DOWN REGULATING DEFENSIN GENE EXPRESSION AND ENHANCING MUCOSAL INFLAMMATION"

Pradeep K. Shukla, Kamaljit K. Chaudhry, Hina Mir, Ruchika Gangwar, Nikki Yadav, Bhargavi Manda, Avtar S. Meena, RadhaKrishna Rao

University of Tennessee Health Science Center, Memphis, TN

Alcohol consumption is a major risk factor for colorectal cancer, but the mechanism involved in this is unknown. We evaluated the effect of ethanol (EtOH) on azoxymethane (AOM)-dextran sulfate sodium (DSS)-induced colonic tumorigenesis in mice. Adult female mice were treated with AOM (10 mg/kg BW) and colitis was induced after 5 days (d) by 3% DSS in drinking water for 5 d. DSS colitis was repeated twice with 15-d intervals. Tumorigenesis was observed at 30 d after the 3rd DSS cycle. During the 15-d intervals and 30 d after 3rd DSS cycle animals were fed Lieber-DeCarli liquid diet with or without 4% EtOH; non-EtOH group were pair fed with isocaloric diet. Colon was examined for tumors, cryosections stained for p-Smad, VEGF and HIF1α. At a precancerous stage, colon was analyzed by microarray analysis and RT-PCR. Cryosections of colon were examined for inflammatory markers, myeloperoxidase (MPO), GR1 (neutrophil) and CD68 (macrophages), by confocal microscopy. EtOH feeding dramatically elevated colonic tumors; both the number and size of tumors were greater. AOM+DSS-induced elevation of p-Smad, VEGF and HIF1α in the colon was greater in EtOH-fed mice. At the precancerous stage, EtOH feeding significantly reduced (46-94% decline) the AOM+DSS-induced expression of defensin genes (Defcr1,3,5,6,20,21,26). EtOH feeding increased the expression of proinflammatory cytokines/chemokines (IL-1α, IL-6, TNFα, CCL5, Cxcl9 and Cxcl10) and elevated MPO, GR1 and CD68-positive cells in the colonic mucosa in AOM+DSS treated mice. This study suggests that chronic EtOH feeding promotes colonic tumorigenesis that is associated with enhanced

mucosal inflammation, suggesting that inflammation play a role in alcohol-mediated promotion of colon cancer.

(28) "ANALYSIS OF 1261 METASTATIC CANCER PATIENTS EVALUATED BY COMPREHENSIVE MOLECULAR PROFILING (CMP) INCLUDING NEXT-GEN SEQUENCING (NGS) FROM A SINGLE INSTITUTION"

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Background: The availability of CMP has increased rapidly, and may be useful in clinical trial matching and making clinical treatment decisions. We sought to standardize the approach to CMP across all providers at a single institution, using an external vendor, and defining tumor types and point of entry into CMP. Methods: We obtained tumor CMP for first line metastatic cancer patients starting in mid 2014. Multi-platform testing included immunohistochemistry, in-situ hybridization, and NGS, with panels ranging from 44 hot spot genes to 592-gene whole exome coverage. We report only on presumed pathogenic mutations, and did not include variants of unknown significance. We opened multiple basket trials for specific molecular targets including PIK3CA, BRAF, FGFR and HER-2-Neu. Results: Results were obtained from 1261 tumor samples. There was not enough tissue for NGS in 7% of submitted samples. Regarding the individual patient mutational burden by NGS, 399 had 0, 391 had 1, 289 had 2, 179 had 3-5, and 3 had > 5 presumed pathogenic mutation. Across all tumors types a PIK3CA mutations was identified in 11% and a BRAF in 6%. In endometrial cancer, there were 27% PIK3CA and 29% PTEN mutations, while pancreatic had CDKN2A mutations in 25%. 33% of all tumors overexpressed c-MET by IHC. PDL-1 was positive (>5% by IHC) in 16% and varied with tumor type: 14% in esophageal, 16% in kidney, 21% in lung, 34% in melanomas and 36% in sarcoma. Conclusions: CMP for patients with advanced cancer can yield actionable information for both standard of care practice as well as prospective identification for clinical trials requiring specific molecular alterations.

(29) "RESTORATION OF MIR-205 ATTENUATES GROWTH AND CHEMO-SENSITIZATION OF PROSTATE CANCER CELLS: A NOVEL NANOPARTICLE APPROACH"

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Prostate cancer is the most common male malignancy among men in the United States. Recent studies suggest that low expression of miR-205 was found in PrCa cells and tumors in comparison to normal prostate epithelial cells. Additionally, seminal studies have shown that restoration of miR-205 in prostate cancer cells resulted in suppression of cell growth, repression of epithelial to mesenchymal-transition, and chemosensitization. However, due to the poor pharmacological kinetics and low in vivo stability of miR-205, serious limitations at the clinical level are being confronted. Therefore, we have chosen a novel nanoparticle-based approach to deliver miR-205, for improved therapeutic benefits in PrCa. A novel miR-205 nanoparticle formulation (termed as miR-MPG) was generated which is composed of an iron oxide core layered with poly(ethylene imine) (PEI), and NHS-PEG-NHS (PEG) polymer. This miR-MPG formulation exhibited optimal particle size and 5.26 mV zeta potential. 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 ratified with respect to concentration of anionic molecules and in a time-dependent manner. We observed no hemolysis during miR-MPG interaction with the RBC indicating its hemocompatibility. In addition, miR-MPG particles exhibited superior internalization and endosmal 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, and the chemoresistance-associated proteins PSMA and MDR1. Real time PCR studies showed induced expression of the miR-205 gene and affected the expression of its downstream genes, such as ZEB1 and MED1. Overall, these results suggest that miR-MPG formulation may serve as a potential candidate to deliver miRNAs.

(30) "TETRASPANIN 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

(31) "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. Inhibitors of MMP-9 activity or down regulation of its expression by siRNA and ribozyme have shown to reduce growth of primary tumor and onset of distant metastases in preclinical animal studies, and significantly increase progression-free survival in patients with inoperable gastric cancer. 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 enzymes (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 a single injection of anti-MMP-9 DNAzyme (AGBD) is sufficient to reduce the size of intracranial 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 could be used as a novel therapeutic agent to fight cancer.

(32) "POPULATION PHARMACOKINETICS OF CARBOPLATIN IN DOGS"

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Introduction: Precise dosing of anticancer drugs is difficult due to the proximity between effective and toxic doses. Carboplatin is an anticancer drug commonly used in the treatment of a variety of solid tumors in dogs. The objective of this study was to explore the pharmacokinetics (PK) of this drug in a population of canine oncology patients, with particular attention to the size and sources of PK variability. Materials: This study included 82 cases of dogs treated at our Veterinary Teaching Hospital for a variety of malignancies during a 4-year period. Doses were administered by a 20 min CRI at 200-300 mg/m2 (1-12.5 mg/kg). Blood samples were collected at the start of the infusion and then at several times during the following 8 hours, averaging 5 samples per dog. Samples were analyzed by HPLC. Clinical and demographical covariates were recorded from each case. Data were analyzed using Monolix 4.1.2 Software (Lixoft SAS, Orsay, France). Results: Data were best fit by a monocompartmental model with zero order input and proportional intra- and inter-individual variability. Population parameter and variability estimates of Vd and Cl were 3.4 L (64% CV) and 57 ml/min (56% CV), respectively. Residual CV was 24.5%. Clearance was correlated with body weight (BW) and body surface area (BSA), but not with age or gender. Volume was correlated with BW, BSA, age and hyperthermia. PK parameter values were more closely correlated with BSA than with BW. The inclusion of BSA decreased the inter-individual variability by 45%. The inclusion of BW0.78 decreased the inter-individual variability by 50% Conclusion: The results of our study confirmed large inter-individual variability for carboplatin in dogs and a larger improvement in the fit associated to BW0.78 than to BSA. The model obtained in this study should allow more accurate prediction of carboplatin clearance in dogs, and hence doses required to achieve target AUC values.

(33) "A THIN TISSUE SAMPLING SYSTEM FOR SEPARATION-COUPLED SPATIALLY RESOLVED CHEMICAL ANALYSIS"

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Described here are the results from the profiling of drugs in dosed mouse thin tissues and proteins arginine vasopressin (AVP) and adrenocorticotropic hormone (ACTH) from normal human pituitary gland and pituitary adenoma tissue sections using a fully automated droplet-based liquid microjunction surface sampling-HPLC-ESI-MS/MS system for spatially resolved sampling, HPLC separation, and mass spectral detection. Quantitation of adjacent mouse tissue sections of different organs and of various thicknesses by droplet-based surface sampling in comparison to bulk extraction of tissue punches showed that extraction efficiency was incomplete using the former method, and that it depended upon the organ and tissue thickness. However, once extraction efficiency was determined and applied, the droplet-based approach provided satisfactory quantitation accuracy and precision for assay validations. In addition, excellent correlation was found between the protein distribution data obtained with this droplet-based liquid microjunction surface sampling-HPLC-ESI-MS/MS system and those data obtained with matrix assisted laser desorption ionization (MALDI) chemical imaging analyses of serial sections of the same tissue. The protein distributions correlated with the visible anatomic pattern of the pituitary gland. AVP was most abundant in the posterior pituitary gland region (neurohypophysis) and ATCH was dominant in the anterior pituitary gland region (adenohypophysis). The relative amounts of AVP and ACTH sampled from a series of ACTH secreting and non-secreting pituitary adenomas correlated with histopathological evaluation. ACTH was readily detected at significantly higher levels in regions of ACTH secreting adenomas and in normal anterior

adenohypophysis compared to non-secreting adenoma and neurohypophysis. AVP was mostly detected in normal neurohypophysis as anticipated.

(34) "SYNTHETIC AND EXPERIMENTAL CAPABILITIES TO ADVANCE CANCER RESEARCH"

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Our research includes development of a synthetic platform to design polymer-based drug delivery systems capable of delivering hydrophobic, hydrophilic drugs, and proteins. Specifically, we developed a method to produce nanogel particles by a controlled chemoenzymatic oxidation of iron(II) cations using at lower concentration of alginate. This method results in formation of nanoparticles that are tunable in size and have monodisperse size distribution. We demonstrated that these particles are suitable for encapsulation of hydrophilic drugs and proteins. Furthermore, we demonstrated a successful synthesis of biocompatible block polymers that can be used for encapsulation of hydrophobic drugs.

Another direction of our research includes development of techniques that can be used for early detection of different diseases. In literature It has been shown that the decrease in elasticity and change in chemical composition of various cells can contribute to onset or/and progression of various diseases including cancer. In our lab we use several techniques to measure mechanical properties and chemical composition. Atomic Force Microscopy is nanoscale technique capable to detect changes of mechanical properties with sensitivity suitable for early stage disease detection. Brillion light scattering is non-invasive and non-destructive method to detect mechanical properties of biomaterials. We demonstrated its applicability to measure mechanical property of a virus. Tip-Enhanced Raman Spectroscopy is non-invasive and non-destructive method to detect chemical composition at the nanoscale important technique to study drug induced chemical changes in biological materials.

Notes

Sketchpad

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