THE OHIO STATE UNIVERSITY
COLLEGE OF PHARMACY

RESEARCH DAY 2012

THURSDAY, MAY 17, 2012
4-H CENTER

Table of Contents

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Welcome from the Dean

May 17, 2012

The College of Pharmacy Research Day is an annual event held to showcase our research activities within our college. Research is a major enterprise of the College of Pharmacy, and covers an extensive array of areas in the pharmaceutical sciences. Faculty, graduate students, professional students, residents, undergraduates, and research staff are extensively involved in the exciting process of discovery and dissemination of knowledge. This year's Research Day is one of the many activities in our College that promotes interdisciplinary discussions and interactions for knowledge exchange.

The College of Pharmacy Research Day 2012 includes a symposium and poster presentations of current research projects by current students and researchers. This year we are pleased to host two distinguished speakers for the symposium. Andrew Dahlem, PhD, Vice President and Chief Operating Officer, Lilly Research Laboratories, will discuss "The Future of Drug Innovation." Horace Loh, PhD, Regents Professor, Frederick and Alice Stark Professor, and Head, Department of Pharmacology, University of Minnesota, will provide a lecture entitled "Our Search for the Ideal Analgesic in Pain Treatment."

The depth and breadth of the research being performed in our college is outstanding. It is indeed exciting to see the results of strong disciplinary and interdisciplinary projects.

Sincerely,

Robert W. Brueggemeier, PhD
Professor and Dean
The Ohio State University College of Pharmacy

Agenda

Thursday, May 17, 2011

11:00 AM - NOON	Participant Set Up
12:30 – 2:00	Poster Presentations and Judging
2:00 – 3:00	*The Future of Drug Innovation* Andrew Dahlem, PhD Vice President & Chief Operating Officer Lilly Research Laboratories
3:00 – 3:30	Reception
3:30 – 4:30	*Our Search for the "Ideal Analgesic" in Pain Treatment* Horace Loh, PhD Regents Professor, Frederick and Alice Stark Professor, and Head Department of Pharmacology, University of Minnesota
4:30 – 4:45	Poster Competition Award Presentations
4:45 – 5:00	Participants Retrieve Posters

About the Speakers

Andrew M. Dahlem, PhD, was named vice president and chief operating officer for Lilly Research Laboratories in February 2007. He had been vice president of toxicology, drug disposition, pharmacokinetics, and Lilly Research Laboratories in Europe since January 2003 and a member of Lilly's Senior Management Council since 2005.

Dahlem received a Bachelor of Science from The Ohio State University in 1982 and a doctorate in toxicology from the Veterinary College of the University of Illinois at Urbana-Champaign in 1989. He currently serves as adjunct professor of toxicology in the College of Veterinary Medicine at Purdue University, the University of Illinois at Urbana-Champaign, and at The Ohio State University. He is also a member of The Ohio State University College of Pharmacy Corporate Council.

Horace Loh earned his PhD in biochemistry in 1965 from the University of Iowa and completed a postdoctoral fellowship in pharmacology (with Eddy Leong Way) at the University of California-San Francisco. After twenty years on the faculty at UCSF Medical Center, Loh accepted the headship in the Department of Pharmacology at the University of Minnesota in 1989 and was named the Frederick and Alice Stark Professor in Neuroscience. Throughout his career, he has published over 400 original research papers and has mentored approximately 100 postdoctoral fellows and 30 PhD students.

Loh's laboratory continues its long-term investigations into the molecular neurobiology of opioid actions and addiction. Current projects include studies on 1) the molecular mechanisms of opiate and endorphin actions; 2) the molecular mechanisms of opiate tolerance; 3) Tissue-specific regulation of opioid receptor gene expression; 4) Regulation of opioid receptor signal transduction; and 5) Functions of endorphins in the CNS.

Posters

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Faculty

TRANSGENIC EXPRESSION OF NRF2/MAFK PROTECTS FOREBRAIN NEURONS FROM EXCITOTOXIC NEURONAL DEATH IN VIVO
Hee-Yeon Cho[1], Karl Obrietan[2], Kari R. Hoyt[1]
[1]College of Pharmacy, The Ohio State University; [2]College of Medicine, The Ohio State University
Presenting Author: Kari Hoyt
Program of Presenting Author: Division of Pharmacology
Poster Number and Abstract Page: 1

NOREPINEPHRINE POTENTIATING EFFECTS OF (-)-COCAINE AND RELATED TROPANE ANALOGUES ON THE ISOLATED RAT VAS DEFERENS
Popat Patil[1], Richard C. Effland[2], Jules B. LaPidus[1],
[1]College of Pharmacy, The Ohio State University; [2]Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ
Presenting Author: Popat Patil
Program of Presenting Author: Division of Pharmacology
Poster Number and Abstract Page: 2

RATES OF VASCULAR RELAXATION BY ANTAGONISTIC DRUGS
Tatiana F. González-Cestari[1], Robert Stearns$_2$, Popat N. Patil[1]
[1]College of Pharmacy, The Ohio State University; [2]The Ohio State University Alumnus
Presenting Author: Popat Patil
Program of Presenting Author: Division of Pharmacology
Poster Number and Abstract Page: 3

MYELOPEROXIDASE (MPO)-DEPENDENCY FOR DNA TOPOISOMERASE II ALPHA AND BETA INHIBITION INDUCED BY THE PHENOLIC ANTICANCER AGENT ETOPOSIDE: IMPLICATIONS FOR ETOPOSIDE-INDUCED LEUKEMOGENESIS
Ragu Kanagasabai[1], Sureshkumar[2], Jack C. Yalowich[1]
[1]College of Pharmacy, The Ohio State University; [2]The Ohio State University Alumnus
Presenting Author: Jack Yalowich
Program of Presenting Author: Division of Pharmacology
Poster Number and Abstract Page: 4

Graduate (MS, PhD)

ROLE OF TUMOR SUPPRESSIVE MICRORNAS IN PANCREATIC DUCTAL ADENOCARCINOMA.
Ana Clara Azevedo-Pouly[1], Jinmai Jiang[1], Eun Joo Lee[1], Vincenzo Coppola[2], Gerard J. Nuovo[3], David Allard[4], David A. Tuveson[4], Thomas D. Schmittgen[1]
[1]College of Pharmacy, The Ohio State University; [2]Comprehensive Cancer Center, The Ohio State University; [3]Phylogeny; [4]Cambridge University
Presenting Author: Ana Clara Azevedo-Pouly
Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Sciences
Poster Number and Abstract Page: 5

IBANDRONATE AND VENTRICULAR ARRHYTHMIA RISK
Ingrid M. Bonilla[1], Pedro Vargas-Pinto[1], Yoshinori Nishijima[1], Adriana Pedraza-Toscano[1], Hsiang-Ting Ho[1], Victor Long[1], Robert L Hamlin[2], Sandor Gyorke[1], Cynthia Carnes[1]
[1]College of Pharmacy, The Ohio State University; [2] Qtest Labs, Columbus, Ohio
Presenting Author: Ingrid Bonilla
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 6

CYTOTOXICITY-GUIDED ISOLATION OF FLAVONOIDS AND ROTENOIDS FROM INDIGOFERA SPICATA
Lynette Bueno Pérez[1], Li Pan[1], Tran Ngoc Ninh[2], Hee-Byung Chai[1], Djaja Djendoel Soejarto[3], David M. Lucas[4,1], A. Douglas Kinghorn[1]
[1]College of Pharmacy, The Ohio State University; [2]Vietnamese Academy of Science and Technology, Vietnam; [3]College of Pharmacy, University of Illinois at Chicago; [4]College of Medicine, The Ohio State University
Presenting Author: Lynette Bueno Perez
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 7

DESIGN, SYNTHESIS, AND BIOLOGICAL STUDIES OF NOVEL SURVIVIN INHIBITORS
Somsundaram Chettiar[1], James Cooley[2], Deepak Bhasin[1], In-Hee park[1], May Mok[1], Chenglong Li[1], Jacob Naduparambil[2], Arnab Chakravarti[2], Pui-Kai Li[1]
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Presenting Author: Somsundaram Chettiar
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 8

T315, A NOVEL INTEGRIN-LINKED KINASE INHIBITOR, SUPPRESSES HYPOXIA-INDUCED EPITHELIAL-TO-MESENCHYMAL TRANSITION IN PROSTATE CANCER
Chih-Chien Chou, Su-Lin Lee, Samuel K. Kulp, Ching-Shih Chen
College of Pharmacy, The Ohio State University
Presenting Author: Chih-Chien Chou
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 9

DIFFERENTIAL ANTI-PROLIFERATIVE ACTIVITIES OF POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS IN TRIPLE-NEGATIVE BREAST CANCER CELLS

Hsiao-Ching Chuang, Naval Kapuriya, Samuel K. Kulp, Charles L. Shapiro, Ching-Shih Chen,
College of Pharmacy, The Ohio State University
Presenting Author: Hsiao-Ching Chuang
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 10

BINDING OF HUMAN IMMUNODEFICIENCY VIRUS COFACTOR TO CHROMATIN

Jocelyn O. Eidahl[1], Brandon Crowe[2], Matt Plumb[1], Justin North[3], Christopher McKee[1], Micheal Poirier[3], Mark Foster[2], Mamuka Kvaratskhelia[1],
[1]College of Pharmacy, The Ohio State University; [2]Department of Biochemistry, The Ohio State University; [3] Department of Biophysics, The Ohio State University
Presenting Author: Jocelyn Eidahl
Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Chemistry
Poster Number and Abstract Page: 11

THE ROLE OF MICRORNA-205 IN BREAST CANCER

Ola Elgamal, Thomas D. Schmittgen, Jong-Kook Park,
College of Pharmacy, The Ohio State University
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Poster Number and Abstract Page: 12

ANTICANCER ACTIVITY AND SAR STUDIES ON VARIOUS SUBSTITUTED NAPHTHOQUINONES

Jonathan Etter, Deepak Bhasin, Somsundaram Chettiar, May Mok, Pui-Kai Li
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Poster Number and Abstract Page: 13

ELECTROSPRAY ENCAPSULATION OF SUBUNIT VACCINES IN POLYMER MICROPARTICLES

Tony D. Duong[1], Sadhana Sharma[2], Kevin Peine[3], Gaurav Gupta[4], Abhay Satoskar[4], Matthew D. Gallovic[2], Eric M. Bachelder[2], Barbara E. Wyslouzil[1], Kristy M. Ainslie[2],
[1]College of Engineering, The Ohio State University;[2]College of Pharmacy, The Ohio State University; [3]Molecular, Cellular, and Developmental Biology, The Ohio State University; [4]College of Medicine, The Ohio State University
Presenting Author: Matthew Gallovic
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Poster Number and Abstract Page: 14

THE NOVEL PROTEASOME INHIBITOR CARFILZOMIB FUNCTIONS INDEPENDENTLY OF P53 AND NF-KB TO INDUCE POTENT CYTOTOXICITY IN PRIMARY CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

Sneha Gupta[1], Ellen Sass[2], Erin Hertlein[2], Jason Dubovsky[2], Rosa Lapalombella[2], Jennifer Woyach[2], Amy Lehman[3], David Jarjoura[3], John C Byrd[1,2], David M Lucas[1,2],
[1]College of Pharmacy, The Ohio State University;[2] College of Medicine, The Ohio State University;
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Presenting Author: Sneha Gupta
Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Chemistry
Poster Number and Abstract Page: 15

PHARMACOKINETICS AND BLOOD-BRAIN BARRIER PENETRATION OF BENDAMUSTINE IN PATIENTS WITH BRAIN METASTASES FROM SOLID TUMORS

Lei He[1], John Grecula[2], Yonghua Ling[1], Xiaoxia Yang[1], Michael Enzerra[1], Jeffrey Cotrill[1], Mario Ammirati[2], Kari Kendra[2], Robert Cavaliere[2], Nina Mayr[2], John McGregor[2], Thomas Olencki[2], Ennio Chiocca[2], James Elder[2], Mani Matharbootham[2], Tim Lautenschlaeger[2], Chimo Oluigbo[2], Barbara McCracken-Bussa[2], Laura Mayer[2], Lai Wei[2], Mitch Phelphs[1]
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Presenting Author: Lei He
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Poster Number and Abstract Page: 16

THE NOVEL ROLE OF INTEGRIN-LINKED KINASE IN IL-6 INDUCED TUMORIGENESIS

En-Chi Hsu[1], Yu-Chou Tseng[1], Yo-Ting Tsai[1], Su-Lin Lee[1], Nicholas J. Sullivan[2], Tatiana M. Oberyszyn[2], Samuel K. Kulp[1], Ching-Shih Chen[1]
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Poster Number and Abstract Page: 17

OSCILLATING AQUEOUS GEL SYSTEMS

Tien-Lu Huang, Sylvan G. Frank
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Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Chemistry
Poster Number and Abstract Page: 18

SYNTHESIS AND NMR ANALYSIS OF O-CLOSO-CARBORANE DERIVATIVES

Keisuke Ishita, Ahmed Khalil, Rohit Tiwari, Werner Tjarks
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Poster Number and Abstract Page: 19

ACTIVATION OF SILENCED TUMOR SUPPRESSOR GENES IN PROSTATE CANCER CELLS BY A NOVEL ENERGY RESTRICTION-MIMETIC AGENT

Yi-Chiu Kuo[1], Hsiang-Yu Lin[2,3,1], Yu-I Weng[4], I-Lu Lai[1], Tim H.-M. Huang[4], Shuan-Pei Lin[3], Dau-Ming Niu[2], Ching-Shih Chen[1],
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Poster Number and Abstract Page: 20

IDENTIFICATION OF CHARAPTERIZATION OF NOVEL INTEGRIN-LINKED KINASE INHIBITOR

Su-Lin Lee, En-Chi Hsu, Chih-Chien Chou, Hsiao-Ching Chuang, Samuel K. Kulp, Ching-Shih Chen
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Poster Number and Abstract Page: 21

BIOACTIVITY-GUIDED ISOLATION OF ANTIOXIDANT AND QUINONE REDUCTASE-INDUCING CONSTITUENTS FROM ARISTOTELIA CHILENSIS (MAQUI BERRY)

Jie Li[1], Hee-byung, Chai[1], Ye, Deng[1], William. J., Keller[2], A. Douglas, Kinghorn[1]
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Poster Number and Abstract Page: 22

ANTILEISHMANIAL ACTIVITY OF A BISBENZYLISOQUINOLINE ALKALOID FROM THE ROOTS OF THALICTRUM ALPINUM

C. Benjamin Naman[1], Gaurav Gupta[2], Claudio M. Lezama-Davila[2], Raymond W. Doskotch[1], Abhay R. Satoskar[2], A. Douglas Kinghorn[1]
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Poster Number and Abstract Page: 23

NF-KB-MEDIATED ZIP8 EXPRESSION CONTRIBUTES TO CD-INDUCED CELL TOXICITY AND EMPHYSEMA IN MICE

Jessica Napolitano[1], Mingjie Liu[2], Shengying Bao[2], Michael Borchers[3], Daniel Nebert[3], Estelle Cormet-Boyaka[4], Patrick Nana-Sinkam[2], Melissa Crawford[2], Daren Knoell[1]
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Presenting Author: Jessica Napolitano
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Poster Number and Abstract Page: 24

ENDOGLIN REGULATES P38 MAPK-INDUCED STRESS FIBER FORMATION AND ENDOTHELIAL MIGRATION

Chris Pan[1], Jeff Bloodworth[2], Mythreye Karthikeyan[3], Arun Sharma[3], Nam Lee[1]
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Poster Number and Abstract Page: 25

UNDERSTANDING THE MECHANISM OF ACTION OF ANTI-LEISHMANIAL ARYLIMIDAMIDE DB766

Trupti Pandharkar[1], Karl Werbovetz[1], Frederick Buckner[2], David Boykin[3],
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Poster Number and Abstract Page: 26

EFFICIENT DELIVERY OF TLR STIMULATORS TO ANTIGEN PRESENTING CELLS USING ACETYLATED DEXTRAN MICROPARTICLES

Kevin Peine[1], Eric Bachelder[1], Zachary Vangundy[1], Tracy Papenfuss[1], Kevin Schully[2], Andrea Keane-Myers[2], Kristy Ainslie[1]
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Poster Number and Abstract Page: 27

REGULATION OF THE MACROPHAGE ZINC TRANSPORTER ZIP8 IN RESPONSE TO MYCOBACTERIUM TUBERCULOSIS INFECTION

Charlie Pyle[1], Larry S. Schlesinger[2], Daren L. Knoell[2]
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Program of Presenting Author: Translational Science
Poster Number and Abstract Page: 28

WATER-IN WATER (W/W) EMULSION SYSTEMS

Anita Sharma, Sylvan G. Frank
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Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Sciences
Poster Number and Abstract Page: 29

ALKALOIDS FROM GREWIA PANICULATA WITH CYTOTOXIC AND NON-COMPETITIVE NICOTINIC RECEPTOR ANTAGONISTIC ACTIVITIES

Patrick Still[1], Tatiana F. González-Cestari[1], Li Pan[1], Hee-Byung Chai[1], James R. Fuchs[1], Tran Ngoc Ninh[2], Djaja Djendoel Soejarto[3], Bitna Yi[1], Brandon J. Henderson[1], Popat N. Patil[1], Dennis B. McKay[1]
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Presenting Author: Patrick Still
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 30

CAVEOLIN-3 REGULATES SUBCELLULAR TARGETING AND FUNCTION OF KIR2.1 CHANNELS

Zhaogang Yang, Chen Kang, Keli Hu
College of Pharmacy, The Ohio State University
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Program of Presenting Author: Division of Pharmacology
Poster Number and Abstract Page: 31

DISCOVERY OF A NOVEL CLASS OF NEGATIVE ALLOSTERIC MODULATORS OF NACHRS AS A POTENTIAL TREATMENT FOR TOBACCO ADDICTION: STRUCTURE ACTIVITY RELATIONSHIP AND MECHANISMS OF ACTION

Bitna Yi[1], Tatiana F. González-Cestari[1], Brandon J. Henderson[1], Martin L. Dalefield[1], Sihui Long[2], Julian Richard[2], Ryan Pavlovicz[3], Karl Werbovetz[1], Chenglong Li[1], R. Thomas Boyd[4], Dennis B. McKay[1]
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Presenting Author: Bitna Yi
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Poster Number and Abstract Page: 32

APPLICATION OF TRANSLATIONAL PK/PD MODELING TO PREDICT OPTIMAL DOSE OF SIRNA NANOPARTICLES

Chenguang Zhou[1], Mitch A. Phelps[1], L. James Lee[2], Robert J. Lee[1]
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Poster Number and Abstract Page: 33

PharmD

IMPACT OF A STUDENT PHARMACIST-RUN HEALTH SCREENING PROGRAM IN MEDICALLY UNDERSERVED AREAS AS AN ENTRY POINT INTO THE HEALTH CARE SYSTEM

Kyle A. Munch[1], Jennifer L. Rodis[1], Kristin A. Casper[1], Catherine H. Kuhn[2], Douglas C. Cornelius[2], Michelle E. Ross[1]
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Poster Number and Abstract Page: 34

Post-Doctoral Researchers

IT TAKES MORE THAN ONE MIRNA TO TREAT HCC

Jon Henry, Jong-Kook Park, Thomas D. Schmittgen
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Poster Number and Abstract Page: 35

SYNTHESIS OF CARBORANYL CONJUGATES OF N3-SUBSTITUTED THYMIDINE AND THEIR EVALUATION AS SUBSTRATES OF RECOMBINANT HUMAN THYMIDINE KINASE 1

Ahmed Khlil[1], Hitesh K. Agarwal[1], Rohit Tiwari[1], Kevin G. Ricks[1], Elena Sjuvarsson[2], Staffan Eriksson[2], Michael V. Darby[1], Werner Tjarks[1]
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Poster Number and Abstract Page: 36

EFFECTS OF (5Z)-7-OXOZEAENOL ON PROSTATE AND BREAST CANCER CELLS

Ulyana Muñoz Acuña [1], Jennifer Wittwer[1], Sloan Ayers[2], Cedric J. Pearce[3], Nicholas H. Oberlies[2], Esperanza J. Carcache de Blanco[1]
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Poster Number and Abstract Page: 37

ISOLATION, STRUCTURE ELUCIDATION, AND BIOLOGICAL EVALUATION OF 16,23-EPOXYCUCURBITACIN CONSTITUENTS FROM ELEAOCARPUS CHINENSIS

Li Pan[1], Yeonjoong Yong[1], Ye Deng[1], Daniel D. Lantvit[2], Tran Ngoc Ninh[3], Heebyung Chai[1], Esperanza J. Carache de Blanco[1], Djaja D. Doejarto[2], Steven M. Swanson[2], A. Douglas Kinghorn[1]
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Presenting Author: Li Pan
Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy
Poster Number and Abstract Page: 38

A PROSPECTIVE, DOUBLE-BLINDED, OBSERVATIONAL CLINICAL COHORT STUDY OF THE ASSOCIATION BETWEEN TACROLIMUS EXPOSURE AND CYP3A4, CYP3A5 GENOTYPES IN ADULT HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Ming Poi[1], Ali Mcbride[2], Jigar Trivedi[2], Julianna Roddy[2], Jiang Wang[3], Danxin Wang[4], Hong Zhu[5], Elizabeth Marek[1], Ee Poi[1], Wolfgang Sadee[4], Steve Devine[4]
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Presenting Author: Ming J. Poi
Program of Presenting Author: Translational Science
Poster Number and Abstract Page: 39

PHARMACOKINETICS OF FLAVOPIRIDOL IN LYMPHOMAS

Ming Poi[1], Jeffrey Jones[2], Amy S. Ruppert[3], Jeffrey Cotrill[3], Jia Ji[1], Diana Chung[1], Niesha Griffith[4], Mitch Phelps[1]

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Program of Presenting Author: Translational Science

Poster Number and Abstract Page: 40

SYNTHESIS OF ELLAGIC ACID PERACETATE AND ANTITUMOR EFFICACY WITH ENHANCEMENT OF IMMUNITY

Yulin Ren[1], Min Wei[2], Patrick C. Still[1], Xiaozhuo Chen[3], Klaus Himmeldirk[3], Michael A. Caligiuri[1], A. Douglas Kinghorn[1], Jianhua Yu[4]

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Presenting Author: Yulin Ren

Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy

Poster Number and Abstract Page: 41

CYTOTOXICITY, NF-KB P65 INHIBITION, AND IN VIVO ANTITUMOR EFFICACY OF SESQUITERPENE LACTONES FROM PIPTOCOMA RUFESCENS

Yulin Ren[1], Ulyana Muñoz Acuña[1], Daniel D. Lantvit[2], Francisco Jiménez[3], Ricardo García[3], Heebyung Chai[1], Judith C. Gallucci[4], Djaja D. Soejarto[2], Esperanza J. Carcache de Blanco[1], Steven M. Swanson[2], A. Douglas Kinghorn[1]

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Presenting Author: Yulin Ren

Program of Presenting Author: Division of Medicinal Chemistry and Pharmacognosy

Poster Number and Abstract Page: 42

Research Staff

IN VIVO QUANTIFICATION OF ACTIVE DECITABINE-TRIPHOSPHATE METABOLITE: A NOVEL PHARMACOANALYTICAL ENDPOINT FOR OPTIMIZATION OF HYPOMETHYLATING THERAPY IN ACUTE MYELOID LEUKEMIA

Hongyan Wang[1], Ping Chen[1], Jiang Wang[1], Ramasamy Santhanam[2], Joesephine Aimiuwu[1], Vijaya Saradhi[1], Zhongfa Liu[1], Sebastian Schwind[2], John C. Byrd[2], Michael R. Grever[2], Miguel A. Villalona-Calero[2], Rebecca Klisovic[2], Allison Walker[2], Ramiro Garzon[2], William Blum[2], Kenneth K. Chan[1], Guido Marucci[1]

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Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Chemistry

Poster Number and Abstract Page: 43

PHARMACOKINETIC AND TISSUE DISTRIBUTION OF SYNTHETIC MIR181A AND ITS IN VITRO BIOTARGETS-MODULATING ACTIVITY

Zhiliang Xie[1], Hongyan Wang[1], Ming Chiu[1], Sebastian Schwind[2], Christopher Hickey[2], Natarajan Muthusamy[2], Guido Marcucci[1], Kenneth K. Chan[1]
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Program of Presenting Author: Division of Pharmaceutics and Pharmaceutical Chemistry
Poster Number and Abstract Page: 44

SIMULTANEOUS QUANTIFICATION OF 5-HYDROXYMETHYL-2'-DEOXYCYTIDINE AND GLOBAL DNA METHYLATION IN DNA USING LIQUID CHROMATOGRAM TANDEM MASS SPECTROMETRY

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Poster Number and Abstract Page: 45

8,8-DIALKYLDIHYDROBERBERINES WITH POTENT ANTIPROTOZOAL ACTIVITY

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Poster Number and Abstract Page: 46

Residents & Fellows

USE OF AN ELECTRONIC MEDICAL RECORD TO IMPROVE CARE AND MONITORING OF CHRONIC KIDNEY DISEASE IN A PATIENT-CENTERED MEDICAL HOME

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Poster Number and Abstract Page: 47

IMPACT OF BARCODE MEDICATION ADMINISTRATION ON EMERGENCY DEPARTMENT ERRORS

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Poster Number and Abstract Page: 48

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Poster Number and Abstract Page: 49

EVALUATION OF PHARMACY FACULTY KNOWLEDGE AND PERCEPTIONS OF THE PATIENT-CENTERED MEDICAL HOME (PCMH) CONCEPT WITHIN PHARMACY EDUCATION

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Poster Number and Abstract Page: 50

DRUG SHORTAGES: MANAGEMENT AND RESPONSE IN HEALTH-SYSTEM PHARMACY

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Poster Number and Abstract Page: 51

MEDICATION EVENT HUDDLES: EFFECT OF AN ELECTRONIC DATABASE ON INTERVENTION FOLLOW-UP IN A PEDIATRIC HOSPITAL

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Poster Number and Abstract Page: 52

PATIENT-CENTERED CARE AT A GENERAL INTERNAL MEDICINE PATIENT-CENTERED MEDICAL HOME

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Poster Number and Abstract Page: 53

PHARMACY RESIDENTS' PURSUIT OF ACADEMIC POSITIONS

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Poster Number and Abstract Page: 54

MEDICATION ERRORS WITH PARENTERAL NUTRITION: IMPACT OF INGREDIENT SHORTAGES

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Poster Number and Abstract Page: 55

EVALUATION OF THE RATES AND CHARACTERISTICS OF ABANDONED PRESCRIPTIONS PRESCRIBED BY FEDERALLY QUALIFIED HEALTH CENTER PROVIDERS AT 340B CONTRACTED COMMUNITY PHARMACIES

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Poster Number and Abstract Page: 56

Undergraduate

ZINC DEFICIENCY IN THE CONTEXT OF OBESITY

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Poster Number and Abstract Page: 57

TREATMENT OF AUTOIMMUNITY THROUGH TOLERANCE

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Poster Number and Abstract Page: 58

PURIFICATION AND IDENTIFICATION OF AN ANTILEISHMANIAL COMPOUND FROM THE ROOTS OF THALICTRUM RUGOSUM

Anthony Gromovsky[1], C. Benjamin Naman[1], Gaurav Gupta[2], Claudio M. Lezama-Davila[2], Raymond W. Doskotch[1], Abhay R. Satoskar[2], A. Douglas Kinghorn[1]
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Poster Number and Abstract Page: 59

SYNTHESIS AND CHARACTERIZATION OF ETHANOL-DEGRADING ACETALATED DEXTRAN POLYMER AND MICROPARTICLES

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Poster Number and Abstract Page: 60

ANTIPSYCHOTIC DRUG IMPACT ON DOPAMINERGIC NEURONS

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Poster Number and Abstract Page: 61

DEPLETION OF PIN1 IN MOUSE AORTIC ENDOTHELIAL CELLS INCREASES INDUCTION OF HYPOXIA-INDUCIBLE TRANSCRIPTION FACTORS

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Poster Number and Abstract Page: 62

IMMUNOSTIMULATORY POLYSACCHARIDES AS A BASE MATERIAL FOR POLYMERIC MICROPARTICLES

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Poster Number and Abstract Page: 63

EVALUATING DRUG THERAPY DECISION MAKING IN PATIENTS WITH EPILEPSY

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Poster Number and Abstract Page: 64

SYNTHESIS OF ALLOSTERIC MODULATORS FOR NICOTINIC ACETYLCHOLINE RECEPTORS

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Poster Number and Abstract Page: 65

TRANSGENIC EXPRESSION OF NRF2/MAFK PROTECTS FOREBRAIN NEURONS FROM EXCITOTOXIC NEURONAL DEATH IN VIVO

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We are examining whether upregulation of neuronal antioxidant response element (ARE) regulated gene expression is neuroprotective in the setting of excitotoxic brain injury. To achieve this goal, we are using a novel transgenic mouse strain that was engineered to express the ARE transcription factors Nrf2 and MafK (and the cell marker eGFP) in neurons in a tetracycline-regulatable manner. We first verified that Nrf2 and gst-1 (a phase II target gene) mRNA expression levels were increased in Nrf2/MafK transgenic mouse brain tissue. To test for a potential neuroprotective role of neuronal Nrf2/MafK expression, we used pilocarpine-induced status epilepticus (SE) to induce excitotoxic damage, and assessed neuronal death and markers of Nrf2 activation 8 and 72 hours post SE. We observed robust SE-induced cell death (measured by fluoro-jade B staining and calpain activation) which was significantly attenuated in Nrf2/MafK transgenic mice compared to wildtype (WT) mice. In Nrf2/MafK transgenic mice, Nrf2 strongly translocated to the nucleus in hippocampal and striatal neurons after excitotoxic stimulation. Induction of the Nrf2-dependent antioxidant gene, HO-1, was assessed by immunoblotting and immunofluorescence labelling in parallel with the cell death assessments. To specifically assess neuronal HO-1 expression, we double-labelled brain tissue with HO-1 and NeuN (a neuronal marker) antibodies. The number of HO-1/NeuN positive cells was 2.5 fold higher in Nrf2/MafK transgenic mice than in WT littermates after SE. In summary, we have established that neuronal Nrf2/MafK upregulation and concomitant detoxifying/antioxidant induction is a viable therapeutic target for the design of therapies to protect neurons from excitotoxic/oxidative injury.

NOREPINEPHRINE POTENTIATING EFFECTS OF (-)-COCAINE AND ITS ANALOGUES RELATED TROPANE ANALOGUES ON THE ISOLATED RAT VAS DEFERENS*

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The natural product Ψ-tropine analogue, (-)-Cocaine, is well known for its norepinephrine potentiating action by inhibiting neuronal uptake at the adrenergic synapse. Related tropine analogue atropine, a potent antimuscarinic, lacks this effect. Actions of tropine and Ψ-tropine analogues were examined to understand the steric structural requirements for the potentiating effect. Rat vas deferens was used as it is very sensitive to drug potentiation. The organ was mounted in the oxygenated tissue bath containing physiological salt solution at 37.5°C. The Control Cumulative Concentration response of the organ to the norepinephrine or the indirectly acting tyramine was obtained. After thorough wash, the tissue was incubated with the drug for 3 minutes, and norepinephrine or tyramine responses were observed. The concentration of the drug that caused ~3-fold shift of the norepinephrine curve to the left was used to compare relative potentiation by analogues. The relative potentiation by drugs were: (-)-Cocaine 1, Tropine benzoate, 1/30th, (+)-Ψ-Cocaine, (±)Allo-Ψ-Cocaine, and Ψ-Tropine benzoate, 1/100th, and Benzoylecgonine, Ψ-Ecgonine methyl ester, (±)-Allo-Ψ-Ecogonine methyl ester, Tropine and Ψ-Tropine, 1/1000th. (-)-Cocaine at 10^{-6}M caused equal shift of the norepinephrine and tyramine dose response curves to the left and right, respectively. Tropine benzoate at $3x10^{-5}$M shifted the curve of norepinephrine by ~3-fold to the left did not change the responses to tyramine. Ψ-Tropine benzoate at 10^{-4}M also potentiated norepinephrine by ~3-fold but markedly inhibited responses to tyramine. Thus these two analogues dissociated the actions of norepinephrine and tyramine (at the transport) in contrast to (-)-cocaine which impacts both actions. Relationship of reactive groups of these molecules to that of the functional effects will be presented.

**In part from the 1971 Ph.D. thesis of R. Effland, is a tribute to our late Jules LaPidus, Professor of Medicinal Chemistry, Dean of Graduate School, who over 40 years ago stimulated our interest in the steric aspects of drug action.*

RATES OF VASCULAR RELAXATION BY ANTAGONISTIC DRUGS

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Majority of mammalian blood vessels are innervated by post ganglionic sympathetic nerves. The activation of the neuron releases (-)-norepinephrine and α-adrenoceptor mediated vasoconstriction is produced. Blockade of this receptor causes vascular relaxation. Many pharmacologic agents as well as endogenous substances produce vascular relaxation by different mechanisms. On the isolated rat aorta, we have investigated the rates of relaxation by the different drugs of phenylephrine- or oxymetazoline-mediated vasospasm. The project was initiated with the idea that comparative relaxation rates should explain the therapeutic rationale for the utility of drugs in vasospastic diseases. In vitro, the α-adrenoceptor activators phenylephrine or oxymetazoline, at approximately EC_{50} concentration, were used to produce a stable contraction of the aorta and, at the response plateau, a concentration of the muscle relaxant drug was added. Rate of vascular relaxation was observed. A number of 3-7 experiments were repeated and data were averaged for calculation of time required for half the initial contraction of the aorta ($T_{1/2}$ values). Blockade of phenylephrine-induced vasospasm with a concentration of phentolamine (100 nM), a competitive reversible α-adrenoceptor antagonist, occurred with a $T_{1/2}$ value of 1.8 min. On the other hand, the irreversible α-adrenoceptor antagonist, dibenamine, caused slow relaxation in the presence of phenylephrine, with $T_{1/2}$ = 11.8 min. The muscarinic cholinergic agonists, carbachol, pilocarpine, and arecoline showed quick relaxation with $T_{1/2}$ values of 0.3, 0.3, and 0.4 min, respectively. The calcium channel antagonist, nifedipine, and phosphodiesterase inhibitors, theophylline and papaverine, exhibited relaxation with $T_{1/2}$ values of 1.8, 0.6, and 2.2 min, respectively. Our results indicate that depending on the mechanism of action of the antagonistic drug, $T_{1/2}$ values for the vascular relaxation vary greatly. Equilibrium studies of vascular relaxation can compromise the importance of one drug over the other in understanding vasospastic mechanisms.

MYELOPEROXIDASE (MPO)-DEPENDENCY FOR DNA TOPOISOMERASE II ALPHA AND BETA INHIBITION INDUCED BY THE PHENOLIC ANTICANCER AGENT ETOPOSIDE: IMPLICATIONS FOR ETOPOSIDE-INDUCED LEUKEMOGENESIS.

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The clinical efficacy of the anticancer agent etoposide (VP-16) is compromised by its ability to cause acute myeloid leukemias (t-AML) associated with *MLL* gene rearrangements. We proposed previously that myeloperoxidase (MPO) found in myeloid precursors converts the phenolic drug VP-16 to its phenoxyl radical (VP-16-O·), which redox cycles, leading to the generation of reactive oxygen species, oxidative DNA damage linked to DNA topoisomerase II (topo II)-mediated strand cleavage, and resultant recombination events causal for t-AML. In the present study we have utilized an shRNA for MPO in myeloid leukemia HL-60 cells to demonstrate MPO dependency for a portion of VP-16 inhibition/poisoning of topo II isoforms. HL-60 cells were infected with lentivirus containing shRNA for GFP or MPO. All infected cell lines grew with similar doubling times (17-19 hr) and contained comparable levels of topo II alpha and beta, and DNA topoisomerase I (topo I). In MPO knockdown cells, mature MPO expression was reduced to 6% of the level found in GFP shRNA controls. MPO activity in cell lysates from MPO shRNA infected cells was reduced to 15% of controls. In HL-60 control cells (GFP shRNA), VP-16 (0-100 μM) induced a progressive increase in DNA double strand breaks assessed by levels of phosphorylated gamma-H2AX. In contrast, VP-16-induced DNA breakage was attenuated in MPO-knockdown cells (shRNA MPO). Using immunoblots of cell lysates, topoisomerase band depletion studies revealed that VP-16-induced topo II alpha- and topo II beta-DNA covalent complexes were decreased in MPO knockdown compared to GFP control cells. VP-16 had no effect on topo I-DNA complexes. In separate studies, direct topo II isoform complexes with genomic DNA were analyzed in GFP shRNA and MPO shRNA infected cells. Using this complementary technique, VP-16-induced topo II-DNA complexes were reduced in MPO knockdown cells compared to shRNA GFP controls. Overall, these new studies, along with previously published work (Mol. Pharmacol. 79(3): 479-497, 2011), implicate MPO-mediated oxidative activation of VP-16 in production of genotoxic and leukemogenic effects known to derive secondary myeloid leukemias after patient treatment with this agent.

ROLE OF TUMOR SUPPRESSIVE microRNAS IN PANCREATIC DUCTAL ADENOCARCINOMA

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microRNAs (miRNAs) are differentially expressed in many cancers including pancreatic ductal adenocarcinoma (PDAC). We performed qPCR profiling studies of primary and mature miRNA in PDAC specimens from patients, pancreatic cancer cell lines and in the pancreas of transgenic KRASG12D transgenic mice. Major deregulation of the miRNAs was seen in the PDAC tumors with 115 of 174 expressed miRNAs (66%) increased in the tumors ($P < 0.05$). Only 5 miRNAs had a pattern of down-regulation from normal to tumor, including the pancreas specific miR-216a, miR-216b and miR-217. Results were corroborated in tissue from two different KRASG12D transgenic mouse models. Tissue specific miRNAs are down-regulated in various cancer types and reverse the malignant phenotype when miRNA mimic oligos are re-introduced into cancer cell lines. In situ hybridization of miR-216/-217 in adult, human pancreas showed that it is expressed most abundantly in acini. We hypothesize that this down-regulated cluster of miRNAs (miR-216a, miR-216b and miR-217) targets epithelial genes and might serve as a gatekeeper for the acinar-to-ductal metaplasia (ADM) seen in PDAC. A three-dimensional ADM cell culture model was employed by culturing primary mouse acini on matrigel. Ductal differentiation, (marked by increasing levels of epithelial markers, decreased levels of acinar markers and duct formation), showed decreasing levels of miR-216a, miR-216b and miR-217. Transfection of a miR-217 oligo mimic into pancreatic cell lines led to a down regulation of KRAS and CDH1 proteins. Epigenetic regulation of the cluster was studied by treating PDAC and pancreas cell lines with 5-aza 2' deoxycytidine and Trichostatin A. Current results show that the mechanism of regulation of these miRNAs does not depend on miRNA biogenesis but might rely on histone methylation. The ability of miR-216a, miR-216b and miR-217 to induce ADM and possibly PDAC will be studied in a miRNA knockout mouse that is currently under development.

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IBANDRONATE AND VENTRICULAR ARRHYTHMIA RISK

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Abstract:
BACKGROUND: Ibandronate is given monthly or quarterly to post-menopausal women to treat or reduce osteoporosis. We report a case of cardiac arrest in an otherwise healthy 55 year old female, 2 weeks after her first dose of ibandronate, with associated hypokalemia and QTc prolongation (575 ms). The QT/QTc remained prolonged after correction of hypokalemia; the QT/QTc returned toward normal after drug discontinuation.
METHODS: A single 3 mg injection was given to four dogs; ECG was monitored for six weeks by telemetry. Langendorff perfused guinea pig hearts were used to evaluate acute ibandronate effects on repolarization. Adult canine ventricular myocytes were used to study action potentials (0.5, 1, and 2 Hz), potassium currents and spontaneous calcium waves during treatment with ibandronate (0.001 - 1000 mcg/L), and washout.
RESULTSs: Three of 4 dogs exhibited increased short-term variability in repolarization only days after the dose. There was no evidence of QT/QTc changes in the Langendorff experiments. In myocytes, ibandronate exposure caused reverse-use dependent prolongation of the action potential (APD50 and APD90), as well as increased beat-to-beat variability in APD90 ($p<0.05$). Early and delayed afterdepolarizations were observed in ~45% of myocytes with ibandronate and in 33% during washout. Notably, ibandronate did not alter Ito, IK1, IKr or IKs. In separate experiments, spontaneous intracellular calcium waves were increased only during washout of ibandronate ($p<0.05$). Buffering calcium with BAPTA prevented ibandronate-induced APD90 instability and afterdepolarizations.
CONCLUSIONS: Ibandronate alters ventricular myocyte electrophysiology and calcium handling to induce cellular arrhythmias; in vivo data is consistent with late onset of torsadogenic repolarization instability. Collectively, these data suggest that abnormalities in myocyte calcium regulation underlie the observed arrhythmias. We conclude that current paradigms to detect proarrhythmia risk may not be sufficiently sensitive.

CYTOTOXICITY-GUIDED ISOLATION OF FLAVONOIDS AND ROTENOIDS FROM INDIGOFERA SPICATA

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Indigofera spicata Forssk. (Leguminosae) is native to parts of East Africa, Madagascar, the Philippines, and Indonesia. However, I. spicata has become widespread in tropical and sub-tropical countries as a ground cover plant.1 The bioactivity-guided fractionation of a cytotoxic chloroform extract of the flowers, fruits, leaves, and twigs of I. spicata, with IC50 values in HT-29 cells of 4.3 µg/mL, in 697 cells of 2.2 µg/mL, and in Raji cells of 5.0 µg/mL, was performed, leading to the isolation of five compounds (1-5). A semi-synthetic compound, (+)-tephrosone (6) was produced by alkaline hydrolysis of (+)-purpurin (1). The structures of these compounds were established on the basis of spectroscopic methods, including NMR and HR-MS, as well as by comparison of their spectroscopic data with those reported in the literature. The structure of the new compound 2 was determined by 1D-, 2D-NMR and HR-MS. The relative configuration of compound 2 was determined by measuring its optical rotation and CD spectrum, and comparing these data to those of compound 1. Compound 4 exhibited potent cytotoxicity for HT-29 and 697 cells, with IC50 values of less than 1 µM. Compound 5 showed cytotoxicity for 697 cells but was inactive against HT-29 and Raji cells. Compounds 1-3, and 6 were inactive for all the cell lines tested. This represents the first report of the isolation of compounds 1-5 from I. spicata. Also, a new compound, (+)-10-deacetyl-purpurin (2) was isolated from this plant. The cytotoxicity of compound 4 has been reported previously using other cancer cell lines but this is the first report of such inhibitory activities for HT-29, 697, and Raji cells. No in vivo studies of compound 4 have been performed so far. This represents a potential candidate lead compound for further studies as a possible anticancer agent.

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DESIGN, SYNTHESIS, AND BIOLOGICAL STUDIES OF NOVEL SURVIVIN INHIBITORS

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Survivin, a member of inhibitors of apoptosis (IAP) protein family is involved in cell division and has anti-apoptotic activity. Survivin is undetectable in non-proliferating cells but is over-expressed in various cancers. Over-expression of survivin in cancer patients has been associated with poor patient survival rates, metastasis, increased recurrence and resistance to radiation therapy and chemotherapy.[1] Thus, survivin is one of the viable molecular targets for the treatment of cancer.

Recently, through HTS-NMR and AS/MS affinity based screenings, Abbott8 was identified to bind to the dimerization interface of survivin.[2] Structure based design approach was used with Abbott8 as the lead structure to design several small molecule inhibitors. The time and dose dependant effects of LLP compounds were compared by tracking green fluorescence signal from GFP-tagged Survivin associated with Chromosomal Passenger Complex (CPC) in HUVEC and PC3cells. Two of the designed inhibitors, LLP3 and LLP9 caused delay in mitosis and imparted major defects in CPC organization and mitotic progression at 50 nM and 100 nM, respectively. Structure-activity-relationship studies will be presented in detail.

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T315, A NOVEL INTEGRIN-LINKED KINASE INHIBITOR, SUPPRESSES HYPOXIA-INDUCED EPITHELIAL-TO-MESENCHYMAL TRANSITION IN PROSTATE CANCER

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Objectives of the study: The epithelial-to-mesenchymal transition (EMT) is an early event in metastasis that involves the loss by epithelial cells of many of their distinctive epithelial characteristics and the acquisition of mesenchymal properties. EMT can be induced in cancer cells by several factors, such as hypoxia and TGF-β1, leading to an aggressive and malignant phenotype. In prostate cancer therapy, EMT can be a major clinical challenge as it can contribute to tumor recurrence, therapy resistance, and metastasis. Recently, the integrin-linked kinase (ILK) has been identified as an important protein involved in the process of EMT by inducing the protein expression and activation of Snail, one of the major EMT markers in various cancer cells. The objective of this study was to evaluate the ability of T315, a novel ILK inhibitor developed in our laboratory, to block hypoxia-induced EMT in prostate cancer cells and to validate the role of ILK in hypoxia-induced EMT.
Methods Used: Western blot analysis was used to assess the effect of EMT inducer (hypoxia and TGF-β1) and T315 on the expression levels epithelial marker, such as E-cadherin and mesenchymal markers including, vimentin, Snail, and Zeb1, in PC-3 cells. Cells were exposed to hypoxic condition (0.5% O2) in a hypoxia chamber (BioSpherix). To clarify that the effect of T315 on EMT was ILK-dependent, stable tranfectants expressing constitutively active (CA)-ILK were used. Immunofluorescence was used to examine the expression and localization of EMT markers. In order to observe the effect of T315 on the motility of PC-3 cells after hypoxia-induced EMT, the Transwell cell migration assay and wound healing migration assay were used. To examine the transcriptional regulation of Snail by HIF1α, luciferase reporter assay and RT-PCR were used to examine Snail promoter activity and mRNA level of Snail in PC-3 cells, respectively. To assess the effect of T315 on Snail phosphorylation and stability, western blotting and immunoprecipitation analysis were used.
Results and Conclusion: Based on the results of western blot analysis and immunofluorescence, EMT was induced by hypoxia and TGF-β1 treatment in PC-3 cells. Moreover, T315 was shown to counteract the effects of hypoxia on EMT markers by efficiently increasing the protein expression level of E-cadherin and decreasing those of HIF1α, vimentin, Snail, and Zeb1 in PC-3 cells. Besides, F-actin immunofluorescence staining also showed the transition of epithelial phenotype to mesenchymal phenotype under hypoxic condition and this phenomenon was reversed by T315 treatment. More importantly, in the Transwell and wound healing migration assays, T315 showed its ability to inhibit hypoxia-induced cell motility in a dose-dependent manner. Western blotting results showed that T315 downregulated PKB/Akt and mTOR activities and decreased HIF1α expression. Furthermore, luciferase report assay revealed that T315 could downregulate Snail promoter activity induced by HIF1α. According to a previous study, GSK3β-mediated Snail phosphorylation altered the nuclear sequestration of Snail and caused Snail to undergo proteasomal degradation. Our western blotting and immunoprecipitation results showed that T315 could cause GSK3β dephosphorylation, increase the phosphorylation status of Snail and promote Snail degradation. Together, these findings suggest that T315 can inhibit hypoxia-induced EMT in PC-3 cells and that this is mediated through the AKT/mTOR/HIF1α pathway.
Significance: These results indicate that the inhibition of ILK can block hypoxia-induced EMT in prostate cancer cells as reflected by changes in molecular markers and cell behavior, and that this inhibition can be achieved by treatment with the novel small molecule agent T315, which may have therapeutic benefits for prostate cancer patients with subsequent metastasis.
Acknowledgement: We thank Su-Lin Lee for T315 synthesis.

DIFFERENTIAL ANTI-PROLIFERATIVE ACTIVITIES OF POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS IN TRIPLE-NEGATIVE BREAST CANCER CELLS

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Objectives of the Study: Triple-negative (ER-negative, PR-negative, HER2/neu-negative) breast cancer (TNBC) is a clinical challenge because of the lack of a specific therapeutic target. Poly (ADP-ribose) polymerase (PARP) is a nuclear enzyme involved in the detection and repair of DNA damage. In DNA repair-defective tumors inhibition of PARP can cause genomic instability and cell death. Currently, four commercial PARP inhibitors [AZD-2281, AG-014699, ABT-888 and BSI-201] are in clinical trials in TNBC. Recent results of a randomized phase II clinical trial showed that BSI-201 when added to platinum-containing combination chemotherapy statistically significantly improved the outcome of metastatic breast cancer patients relative to chemotherapy alone. Despite recent advances in the clinical evaluation of various PARP inhibitors in TNBC patients, *in vitro* data to define potential anti-tumor mechanisms beyond PARP inhibition for these agents are lacking.
Methods: MDA-MB-468, MDA-MB-231 and Cal-51 cells were obtained from ATCC and DSMZ and maintained in complete growth medium. The four PARP inhibitors, AZD-2281, AG-014699, ABT-888 and BSI-201 were evaluated in cell survival assays [MTT and clonogenic formation]. PARP-dependent and-independent signaling mechanisms of each PARP inhibitors were investigated by Western blotting and shRNA-mediated knockdown. Potential synergistic interactions between PARP inhibitors and cisplatin in suppressing TNBC cell viability were assessed.
Results: The four PARP inhibitors exhibited differential antitumor activities, with the relative potencies of AG-014699 > AZD-2281 > ABT-888 > BSI-201. The higher potencies of AG- 014699 and AZD-2281 were associated with their effects on G2/M arrest and DNA damage as manifested by γ-H2AX formation. Abilities of individual PARP inhibitors to sensitize TNBC cells to cisplatin varied to a great extent in a cell context- and cell line-specific manner.
Significance: These studies will contribute to a deeper understanding of potential differences in the PARP inhibitors which is essential for planning preclinical studies of the PARP inhibitors as single agents and in combination with other novel therapeutics.

BINDING OF HUMAN IMMUNODEFICIENCY VIRUS COFACTOR TO CHROMATIN

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HIV-1 replication requires integration of the viral cDNA made by reverse transcription into the host chromosome for viral replication and maintenance of the infected state in the host. The integration step is catalyzed by the retroviral enzyme integrase (IN). *In vivo* this process is regulated by multiple viral and cellular cofactors. Among these, lens epithelium-derived growth factor (LEDGF) has been identified as the principal cellular cofactor essential for effective HIV-1 integration. LEDGF tethers the HIV-1 IN to active transcription units in the host chromatin. The C-terminal region of LEDGF contains the integrase binding domain, IBD, which binds HIV-1 IN. While the N-terminal domain ensemble of LEDGF is essential for chromatin binding, the molecular mechanism of these interactions is unknown. A component of the N-terminal domain ensemble, the PWWP domain, is necessary for interactions to chromatin. Deletion of the PWWP domain causes reduced HIV integration into active transcription units. PWWP domains can be found in over 60 eukaryotic proteins. Of the PWWP containing proteins that have been studied, results show these domains to contain a hydrophobic cavity that recognizes specific core histone post-translational modifications. We hypothesize the PWWP domain of LEDGF recognizes a specific core histone post-translational modification while simultaneously binding HIV-1 IN through its IBD allowing HIV-1 integration to occur in active transcription units. To further understand the interactions between the PWWP domain of LEDGF and chromatin, NMR spectroscopy and various biophysical methods were utilized. NMR spectroscopy was performed to solve the structure of the PWWP domain of LEDGF. Comparison of the HSQC-15N spectra of the domain in the presence and absence of native nucleosomes was done to identify PWWP domain residues interacting with the native nucleosomes. Multiple biophysical methods were used to prove the LEDGF PWWP domain is sufficient for nucleosome binding and directly interacts with the modified core histone proteins. The PWWP domain contains a hydrophobic cavity similar to other known PWWP domain structures. NMR titration experiments of the PWWP domain and nucleosomes identified a region of the protein potentially interacting with nucleosomes. Residues were mapped to the newly solved LEDGF PWWP domain structure and a binding model was proposed involving both protein and DNA interactions. Currently, proteomic-based experiments are being performed to identify the histone core post-translational modification recognized by the LEDGF PWWP domain. Experimental findings have the potential to aid in the development of novel antiretroviral therapies to prevent the spread of HIV infection.

THE ROLE OF MICRORNA-205 IN BREAST CANCER

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Purpose: Breast cancer is one of the leading causes of death in women of all races. Triple negative breast cancer (TNBC) is considered the most challenging type of breast cancer as it has the worse prognosis and can not be targeted with the most currently available treatments. It is crucial to find the molecular changes that cause TNBC. The intent of this study is to investigate the role of microRNA-205 (miR-205) in TNBC.

Methods: miR-205 was measured in five breast cancer cell lines of four different classifications. Classification is based on the expression of estrogen receptor (ER), progesterone receptor (PR) and her2/neu receptor. miR-205 was absent in the TNBC cell lines MDA-MB-231 and BT549. Using the miRNA target program TargetScan, gene X was predicted to have two binding sites for miR-205. miR-205 – gene X interaction was validated by luciferase reporter assay. 2860 base pairs of the gene X 3'untranslated region (3' UTR) was cloned downstream of the luciferase gene. MDA-MB-231 cells were transfected with gene X 3'UTR luciferase construct and precursor miR-205 oligonucleotide (pre-miR-205 oligo) or control oligo.

Results: In this pilot study, miR-205 reduced the expression of the luciferase gene X by 30-fold compared to control oligo.

Conclusion: miR-205 is one of the microRNAs regulating gene X which is reported to have a role in DNA replication and metastasis. Over-expression of miR-205 results in reduced luciferase gene translation. Therefore, miR-205 has a potential role in decreasing metastasis in breast cancer.

ANTICANCER ACTIVITY AND SAR STUDIES ON VARIOUS SUBSTITUTED NAPHTHOQUINONES

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Large numbers of quinones and anthraquinones have been associated with antitumor, antibacterial, antimalarial and antifungal activity. Our initial studies on STAT3 inhibitors led to the discovery of LLL-12 as a potent compound exhibiting antitumor activity. Among the naphthoquinones, LLL-3.1 was found to be the most potent two ring analogue synthesized in that series. In an effort to further analyze the activity and develop the SAR, various compounds based on Juglone, Plumbagin, Menadione have been synthesized. The synthesized compounds were tested on various cancer cell lines such as HT-29, DU-145 and MDA-MB-231 using MTS assay. The details will be presented in detail.

ELECTROSPRAY ENCAPSULATION OF SUBUNIT VACCINES IN POLYMER MICROPARTICLES

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Vaccines are the most effective intervention for the prevention of disease, and subunit (i.e. protein based) vaccines are considered to be the safest. To generate an enhanced T-cell response from a subunit vaccine, researchers have used delivery systems like polymer microparticles in conjunction with an adjuvant. Our laboratory synthesizes microparticles using acetalated dextran (Ac-DEX). Ac-DEX is unique from other biopolymers because it is acid sensitive, its degradation is tunable, and its by-products are pH neutral. The acid sensitivity of Ac-DEX facilitates stability at extracellular pH (7.4) and rapid degradation at acidic conditions. Since the endosomes of antigen presenting cells (APCs) contain toll-like receptors (TLR), whose stimulation results in an adjuvant response, and exist at an acidic pH, Ac-DEX particles are ideal for delivering a TLR agonist to these immune cells. Ac-DEX microparticles have previously been fabricated through emulsion methods. However, severe concentration limits for drug encapsulation are reached for the TLR agonist resiquimod because it can easily partition into the continuous phase of an emulsion. An alternative method for resiquimod encapsulation is electrohydrodynamic spraying (i.e. electrospraying). Electrospray is a method commercially used for ionizing biological molecules for mass spectroscopy, and it is a research technology that continues to be more widely applied in the fabrication of drug delivery vehicles. The electrospray process creates minimal shear stresses, can be optimized to produce a monodisperse population of particles, displays high encapsulation efficiency, and can be operated at ambient conditions. Additionally, it holds the potential to be scaled-up to a continuous commercial process (as opposed to a batch emulsion). Current efforts in our lab have shown the successful encapsulation of resiquimod in Ac-DEX particles using electrospray and promising *in vivo* results for the treatment of leishmaniasis using these particles. Continuing work is being conducted for encapsulating an antigenic protein via electrospray, and future work will co-deliver an adjuvant and antigen, either in a co-encapsulation or separately.

THE NOVEL PROTEASOME INHIBITOR CARFILZOMIB FUNCTIONS INDEPENDENTLY OF P53 AND NF-KB TO INDUCE POTENT CYTOTOXICITY IN PRIMARY CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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Carfilzomib (CFZ) belongs to a new class of irreversible proteasome inhibitors that specifically target the chymotrypsin-like subunit (CT-L) of the 26S proteasome. CFZ is currently in a phase I clinical trial at The Ohio State University in patients with relapsed or refractory CLL, however, the mechanism of action is unknown. Here we demonstrate that a short (1 hr) exposure of 100 nM CFZ is sufficient to inhibit the CT-L subunit in CLL cells. This exposure is also rapidly cytotoxic, inducing apoptosis in approximately 50% of cells by 24 hr. Unlike the reversible proteasome inhibitor bortezomib, the cytotoxicity of CFZ is not diminished in media with human serum compared to fetal bovine serum. Additionally, CFZ is more cytotoxic to normal $CD19^+$ B cells than normal $CD3^+$ T cells at clinically relevant concentrations of 33 to 300 nM. CFZ causes cell death ex vivo by a caspase-dependent apoptotic pathway, indicated by PARP cleavage and rescue by the broad caspase inhibitor Boc-D-fmk. Importantly, our studies indicate that CFZ causes cytotoxicity in primary CLL cells irrespective of p53 status. The NF-kB signaling pathway is broadly implicated in CLL cell survival and proteasome inhibitors have been reported to block this pathway via inhibition of IkB degradation. Paradoxically, our results indicate that CFZ leads to activation of NF-kB, as evidenced by increased nuclear accumulation of the p50 and p65 subunits of NF-kB, as well as phosphorylated IkBα. This correlates with enhanced binding of the p50/p65 heterodimer to an NF-kB probe in an electrophoretic mobility shift assay. However, despite this apparent NF-kB activation, no transcriptional increases were observed in typical NF-kB targets genes. This is the first study suggesting that treatment with a proteasome inhibitor induces a defective NF-κB response in CLL cells. Collectively, our data indicate that proteasome inhibition is a relevant therapeutic target in CLL and supports the development of CFZ for the treatment of CLL.

SYNTHESIS OF ELLAGIC ACID PERACETATE AND ANTITUMOR EFFICACY WITH ENHANCEMENT OF IMMUNITY

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Ellagic acid (EA), commonly found in many fruits of the human diet, has been reported previously to suppress tumor incidence and to inhibit selectively methylbenzylnitrosamine-induced formation of esophageal O^6-methylguanine in rats. Previous studies have shown that ellagic acid peracetate (EAPA) exhibits more potent bioactivities than EA, but a comparison of the antitumor potency of EAPA with that of EA has not been reported. A new synthetic method was developed for the total synthesis of EAPA with α-pentagalloylglucopyranose produced from methyl gallate and hydrolyzed to EA, which was derivatized to EAPA through acetylation. A subcutaneous B16 melanoma tumor model of C57BL/6 immunocompetent mice was used to evaluate the antitumor efficacy of the two chemicals. The treatment of EA and EAPA was initiated a week before tumor inoculation and continued for an additional two weeks, using a dose of 0.5 mg/kg per mouse. After the treatment, tumors were removed, weighed, photographed, and the average tumor size was calculated and compared. The expression of CD107a and the production of IFN-γ in natural killer cells and the levels of white blood cells and other immune cells were determined, with the weights of bodies, livers, and spleens of normal mice also being evaluated. The results showed that administration of EAPA significantly suppressed B16 melanoma growth in immunocompetent mice without affecting natural killer cell activity and was more effective than EA. EAPA increased white blood cell quantity in several organs or tissues including peripheral blood, bone marrow, and liver, and such effects were greater than those of EA. Furthermore, neither compound resulted in any body, liver or spleen weight changes of normal mice, indicating that these agents are non-toxic to mice. This study suggests that EAPA may be investigated further as a new immunity-stimulatory anticancer drug candidate with potential low toxicity for cancer treatment.

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CYTOTOXICITY, NF-κB P65 INHIBITION, AND *IN VIVO* ANTITUMOR EFFICACY OF SESQUITERPENE LACTONES FROM *PIPTOCOMA RUFESCENS*

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Piptocoma is a small genus of the plant family Asteraceae that occurs in tropical and sub-tropical regions of the Western Hemisphere. There are no previous reports on the chemical constituents of any member of this genus. As part of search for new natural product anticancer agents from diverse organisms, a leaf crude methanol extract of *P. rufescens*, collected in the Dominican Republic, was found to be cytotoxic toward the HT-29 human colon cancer cell line. Using column chromatography guided by cytotoxicity to HT-29 cells, several new and known sesquiterpene lactones (SQLs) were isolated from *P. rufescens*. The structures of the SQLs were established from their IR, UV, NMR, and mass spectra, and the absolute configurations were determined by analysis of single-crystal X-ray diffraction, Mosher ester reactions, specific rotation values, NOESY NMR data, and CD spectra. All SQLs were screened in terms of their cytotoxicity against HT-29 cells, and some were tested in a NF-κB p65 inhibition assay. The antitumor potential of three highly cytotoxic SQLs, goyazensolide, 15-deoxygoyazensolide, and ereglomerulide was evaluated in an *in vivo* hollow fiber assay. The results showed that all the SQLs isolated were highly cytotoxic toward HT-29 cells, with 15-deoxygoyazensolide (IC_{50}, 0.26 μM) being the most potently active compound. Several SQLs exhibited NF-κB p65 inhibitory activity. A cytotoxic compound, goyazensolide, showed significant *in vivo* antitumor potency, when tested at a dose of 12.5 mg/kg (i.p.) in mice, but two other SQLs, 15-deoxygoyazensolide and ereglomerulide, were inactive in this *in vivo* assay system, when evaluated up to a dose of 25.0 mg/kg (i.p.) in mice. This study describes for the first time the cytotoxic constituents of *Piptocoma rufescens* and evaluation of the *in vivo* antitumor activity of goyazensolide, which shows potential for further study towards new anticancer drug development.

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IN VIVO QUANTIFICATION OF ACTIVE DECITABINE-TRIPHOSPHATE METABOLITE: A NOVEL PHARMACOANALYTICAL ENDPOINT FOR OPTIMIZATION OF HYPOMETHYLATING THERAPY IN ACUTE MYELOID LEUKEMIA

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Objective of the study: Decitabine (DAC) is used for treatment of myelodysplastic syndrome and acute myeloid leukemia (AML). Following cellular uptake, DAC is activated to DAC-triphosphate (TP) and incorporated into DNA. The DAC-DNA binds DNA methyltransferases (DNMTs), thereby leading to hypomethylation and re-expression of epigenetically silenced genes and ultimately anti-leukemia activity. However, direct evidence of *in vivo* DAC-TP occurrence in DAC-treated patients has been difficult to demonstrate. Thus, we aimed to develop sensitive and specific quantification method for DAC-TP analysis. **Methodology:** liquid chromatography/tandem mass spectrometry (LC/MS) assay for intracellular DAC-TP was developed by adapting method for dNTP/NTP quantification. C57/BL6 and FDC-P1/*Kit*^{mut} cells-engrafted NOD/SCID mice were treated with an *i.v.* bolus dose of DAC at 6.5mg/kg. Bone marrow (BM) and spleen samples were collected 4 or 24 hours after drug administration. Mononuclear cells were obtained from BM of AML patients treated with 20mg/m^2/day DAC intravenously over 1 hour for 10 consecutive days. Protein levels of DNMTs were analyzed by immunoblotting. **Results and Conclusions:** The developed assay exhibited excellent accuracy and precision. Following DAC treatment, we detected DAC-TP in AML cells (*in vitro)* and BM and spleen of normal and leukemic mice (*in vivo)* Downregulation of DNMTs was also demonstrated in cell lines and mice bone marrow. The clinical applicability of this method was further proved by measuring DAC-TP level in BM from five DAC-treated AML patients. The mean DAC-TP levels were 1.0 0.5 and 0.7 0.4 pmol/10^6 cells on day 1 and ~ day 5, respectively. Individual dose variability was also observed. **Significance:** Our assay is the first to determine the DAC-TP *in vivo* Although more extensive studies are needed for correlating DAC-TP levels with disease response and resistance to DAC, the intracellular level of DAC-TP may serve as an early and novel pharmacoanalytical biomarker for designing more effective DAC-based regimens and monitoring onset of resistance in individual DAC-treated AML patient. [Supported by NCI grants UO1-CA76576 (KKC, GM, RBK and WB), NO1-CM-2011-00070 (MAV) and RO1-CA102031 (GM and KKC)]

PHARMACOKINETIC AND TISSUE DISTRIBUTION OF SYNTHETIC MIR181A AND ITS *IN VITRO* BIOTARGETS-MODULATING ACTIVITY

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Objectives of the study: Deregulated microRNAs (miRs) expression contributes to tumor development and progression by altering expression of tumor suppressor gene and oncogenes in acute myeloid leukemia (AML). Restoring downregulated miR or antagonizing overexpressed miR by synthetic RNA oligonucleotides represents a novel therapeutic approach. Our previous studies have shown that downregulation of miR181a resulted in overexpression of components of inflammasome, TLR4 and IL-1β and in turn activates NFκB pathway in AML cells. Indeed, lower miR181a expression is associated with prognostically unfavorable disease. Thus, the use of synthetic 2'-methoxyphosphorothiolate-miR181a (2'-MeOPSmiR181a), either alone or in combination with other molecular targeting compounds and/or chemotherapy to restore its physiological levels in AML cells may represent a potentially novel treatment for AML. Thus, suitable pharmacoanalytical methods that test level and distribution of 2'-MeOPSmiR181a in plasma and other biological matrices are needed for its clinical development.
Methodology: The assay is developed based on a two-step hybridization technique, with synthetic 2'-MeOPSmiR181a binding to a biotin labeled 9-mer longer capture probe followed by detection of fluorescence generated from detection probe linked anti-Dig-alkaline phosphatase system. This method was validated in human THP-1 leukemia cell lysates and mouse plasma. The mRNA and protein level of the molecular targets of 2'-MeOPSmiR181a were analyzed by QRT-PCR and western blot, respectively, 24 hours after introducing this synthetic oligonucleotide into THP-1 cells by nucleofection. Pharmacokinetics (PK) study of 2'-MeOPSmiR181a was conducted in CD2F1 mice following an *i.v* bolus dose of 7.5 mg/kg. The plasma and major organ tissues (bone marrow, spleen, liver, brain, kidney, lung and heart) were collected at 0.08, 0.17, 0.25, 0.5, 1, 2, 4, 8, 24 and 48 hours post-injection. 2'-MeOPSmiR181a levels in mouse plasma and tissues were measured by our developed ELISA and its PK properties were analyzed by using WinNonlin computer software.
Results and conclusion: Excellent linearity was observed in cell lysate and mouse plasma at a concentration range of 10-5000 pM (R2>0.99). In cell lysate, the within-day and between-day coefficient of variations (CVs, n=6) were <10% and <19.5%, respectively, at a concentration range of 50-5000 pM and their corresponding accuracy values were 93-107.4% and 105.7-115.2%, respectively. In mouse plasma, the within-day and between-day CVs (n=6) were <15% and <20% at a concentration range of 50-5000 pM and the accuracy values were 96-104.3% and 93-101.4%, respectively. Our *in vitro* study showed that 2'-MeOPSmiR181a, at 1 μM, could efficiently downregulate the expression level of its bona-fide targets TLR4 and IL-1β in THP-1 cells. We further demonstrated that in mice following *i.v.* bolus dose of 7.5 mg/kg, 2'-MeOPSmiR181a displayed a two-compartmental PK with measured *C5min* of 7.7 μM, *AUC* (area under the curve) of 118.1 min*μM, *Beta-HL* (terminal half-life) of 17 hours and the *CL* (total body clearance) 0.008 L/min*kg. In addition, its tissue levels were measurable from 5 minutes to at least 24 hours after dosing. Of note, the intracellular level of 2'-MeOPSmiR181a in bone marrow mononuclear cells achieved 1.0-2.6 pmol/mg protein (~30nM) during the time that we monitored.
Significance: A novel sensitive quantification assay was developed and applied for characterization of 2'-MeOPSmiR181a PK and tissue distribution in normal mice. Moreover, the *in vitro* targets-downregulating concentrations were achieved in mice plasma *in vivo*. These data indicated that our method is applicable for PK-PD modeling in leukemic mouse treated with 2'-MeOPSmiR181a. This will allow the development and rapid translation of this novel compound into the clinic for AML.
This study is supported by NIH grant R01-CA135332 (KKC, NM and GM).

Simultaneous Quantification of 5-Hydroxymethyl-2'-deoxycytidine and Global DNA Methylation in DNA using Liquid Chromatogram Tandem Mass Spectrometry

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Objectives of the study: 5-Hydroxymethyl-2'-deoxycytidine (5-HmdC) has been identified as a new novel DNA methylation marker and base modification of DNA methylation. However, most established DNA methylation methods are incapable of distinguishing 5-methyl-2'-deoxycytidine (5-mdC) from 5-HmdC. Herein, we developed a LC-MS/MS method for simultaneous quantification of 5-HmdC and 5-mdC in DNA to differentiate these two DNA methylation markers. This method was used to measure genomic DNA methylation level (GDM) and the content of 5-HmdC in somatic tissues and cancer cells.
Methodology: A triple-quadruple mass spectrometry was used to quantify 2'-deoxycytidine (2-dC), 5-mdC, 5-HmdC using 5,6-dihydro-5-azacytidine as the internal standard by monitoring the following ion transition channels (m/z): 228>112, 242>126, 258>142, and 247>115, respectively. The genomic DNA isolated from mouse liver tissues, three leukemia cell lines, two breast cancer cell lines and one pancreatic cancer cell line was hydrolyzed, and the levels of 2-dC, 5-mdC, 5-HmdC in these DNAs were determined using this method.
Results and conclusion: The lower limit of quantification for 2-dC, 5-mdC and 5-HmdC in the hydrolysates was 0.2 ng/mL. The within-day and between-day parameters for the quality control concentrations between 0.2-1000 ng/mL in DNA samples met the US FDA GLP analytical method criteria with CVs < 8% and accuracy in the range of 89% to 107%. In addition to the detection of 1.8 to 10% GDM in these samples, 5-HmdC was also detectable in mouse liver tissues (≤ 1/3 of 5-mdC) and in Kasumi-1 and HL-60 leukemia cell lines and MCF-7, a breast cancer cell line (≤ 1/20 of 5-mdC). However, 5-HmdC was undetectable in the pancreatic cancer cell line, leukemia MV4-11 cell line, and breast cancer MDA-MB-231 cell line. Notably, two-week daily oral administration of 1.8 g/kg curcumin in mice significantly decreased 5-HmdC levels in liver tissues without affecting the GDM.

A specific LC-MS/MS method was established to differentiate GDM and 5-HmdC in DNA samples, which is an important tool for future DNA methylation analysis.

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8,8-DIALKYLDIHYDROBERBERINES WITH POTENT ANTIPROTOZOAL ACTIVITY

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The plant quaternary alkaloid berberine continues to be investigated for a host of biological effects, including anticancer, antidiabetic, and anti-infective activity. We recently identified a novel semisynthetic berberine derivative, 5,6-didehydro-8,8-diethyl-13-oxodihydroberberine, that displayed potent antileishmanial, antitrypanosomal and antimalarial activity and showed efficacy in a murine visceral leishmaniasis model.[1] However, this compound was toxic to mice when given at i.p. doses higher than 1 mg/kg/day. We prepared analogs of 5,6-didehydro-8,8-diethyl-13-oxodihydroberberine in an attempt to explore the antiparasitic structure-activity relationship of the class and to reduce the in vivo toxicity of the lead compound. These analogs were prepared in three or four steps starting from berberine. Semisynthetic 8,8-dialkyldihydroberberines (8,8-DDBs) possess mid- to low-nanomolar potency against *Plasmodium falciparum* blood-stage parasites, *Leishmania donovani* intracellular amastigotes, and *Trypanosoma brucei brucei* bloodstream forms. 8,8-Dialkylcanadines, obtained by reduction of the corresponding 8,8-DDBs, are much less potent against these parasites in vitro. 8,8-DDBs show efficacy in a mouse model of visceral leishmaniasis and are less toxic than the lead compound. 8,8-DDBs may thus be useful in discovering new antimalarial, antileishmanial, and antitrypanosomal drug candidates.

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USE OF AN ELECTRONIC MEDICAL RECORD TO IMPROVE CARE AND MONITORING OF CHRONIC KIDNEY DISEASE IN A PATIENT-CENTERED MEDICAL HOME

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Purpose: The purpose of this study is to use the electronic medical record (EMR) and pharmacist intervention to identify patients with stage 3, 4, or 5 CKD and improve care within a patient-centered medical home. Objectives of the study are to increase compliance with the National Kidney Foundation guidelines for monitoring and care of CKD, ensure appropriate dosing of medications based on patient's calculated creatinine clearance, determine the percentage of pharmacist recommendations accepted by the patient's primary care physician (PCP), and track pharmacist time spent completing the intervention.
Methods: The EMR will generate a list of adult patients with an estimated glomerular filtration rate <60 mL/min/1.73mm^2. A retrospective chart review of identified patients will be performed to: 1) confirm presence of CKD in patients with criteria for stage 3, 4 or 5 CKD, 2) assess completion of recommended laboratory monitoring and medication therapy for CKD, and 3) assess appropriate dosing of medications. Pharmacist recommendations for care will be communicated with the patient's PCP; patients will be contacted if laboratory measures or medication changes are recommended.
Preliminary Results: 201 (11.3%) patients with CKD were identified through EMR generated reports with 54.2% of patients not having CKD listed as a medical problem in the EMR prior to pharmacist intervention. Improvement in all recommended laboratory monitoring and medication therapy occurred as a result of pharmacist intervention. Additionally, 0.86 medications per patient were dosed inappropriately or contraindicated based on the patient's renal function; 90.2% of medication recommendations made by the pharmacist were accepted by the patient's PCP.
Conclusions: Opportunities for the improvement in identification and care of CKD in a primary care setting exist. Pharmacists are well positioned to work with PCPs to improve CKD care, monitoring, and medication dosing. Future completion of this study will allow for integration and sustainability of outpatient renal dosing services into primary care settings to improve patient outcomes.

Maria Joy, Ashley Shumaker, The American Society of Health-System Pharmacists Research and Education Foundation

IMPACT OF BARCODE MEDICATION ADMINISTRATION ON EMERGENCY DEPARTMENT ERRORS

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The medication use system is error prone with medication administration accounting for 34-54% of medication errors. Barcode medication administration (BCMA) improves the accuracy of medication administration in hospital inpatients, but has limited use in emergency departments (ED); this is due to short lengths of ED stay and limited use of electronic medical records (EMR). The Ohio State University Medical Center implemented an EMR and BCMA in the ED, allowing the opportunity to study the impact of this technology on medication administrations errors.

A single-center, pre/post observational study was conducted to compare medication administration errors after implementing BCMA. Naïve observers documented medication administration 2 months prior to and 4 months post BCMA. A medication administration error was defined as any discrepancy between the administered medication and the physician's order. The primary aim of this study, the medication administration error rate, was calculated by dividing the number of medication administration errors by the number of medication observations. A secondary aim compared medication administration errors to the time of day and therapeutic class. Medications administered by non-nursing staff were excluded from observation. Pre and post medication administration error rates are compared using a 2 proportion z-test; time of day and medication category differences are calculated using linear regression.

996 medication observations were conducted in the baseline period with an error rate of 6.0%. 956 observations are planned in the post BCMA study period.

Conclusions and results will be presented after data collection and evaluation is complete.

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IMPACT OF AN AUTOMATIC REFILL SYSTEM ON MEDICATION POSSESSION RATIOS IN THE COMMUNITY PHARMACY SETTING

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Medication adherence is directly associated with improved clinical outcomes. Therefore, it is crucial to ensure that pharmacists encourage patients to remain adherent through available channels. Enrollment of patients in an automatic refill system aims to improve medication adherence by making it easier for patients to fill their medications on time. One useful way to measure this impact is through the medication possession ratio (MPR) which is defined as the ratio of the number of days between the last refill and the next expected refill to the number of days between the last refill and the next actual fill. Retrospective data will be collected for a random sample of patients enrolled in the automatic refill system at a community pharmacy chain. MPRs will be calculated for six months before and after enrollment to assess the impact of the automatic refill system. Specific disease states for comparison include hypertension, dyslipidemia, diabetes, depression, asthma/COPD, and gastroesophageal reflux disease. Demographic data of patients including age, gender, insurance coverage, number of chronic medications, and method of refill notification will also be collected and analyzed. Data collection will take place in February and March of 2012. Results will provide information to identify potential areas for improvement in counseling and patient care programs that may enhance adherence and patient outcomes.

EVALUATION OF PHARMACY FACULTY KNOWLEDGE AND PERCEPTIONS OF THE PATIENT-CENTERED MEDICAL HOME (PCMH) CONCEPT WITHIN PHARMACY EDUCATION

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Objectives: The Patient Protection and Affordable Care Act of March 2010 emphasizes the need for a reorganized primary care system and supports patient centered medical home (PCMH) as a primary care initiative. Future pharmacists have an important opportunity to advance practice through PCMH practices, and pharmacy education has a central responsibility in preparing pharmacists to effectively contribute in this setting. This project aims to 1) assess pharmacy faculty knowledge about key PCMH principles, 2) evaluate pharmacy faculty perception of inclusion of PCMH information in didactic and/or experiential pharmacy curriculum, and 3) evaluate pharmacy faculty perception of where and how this information should be taught. Methods: A roster of current pharmacy faculty has been obtained from the American Association of Colleges of Pharmacy (AACP) and used to create a database of potential participants. A customizable survey program was used to develop and implement an anonymous, online survey. The survey was pilot tested by a group of non-AACP faculty members, and refined based on input. Faculty rated their familiarity with key PCMH definitions and principles. Participants indicated whether or not PCMH concepts are currently included and should be included in pharmacy education and if so, where in the curriculum, required or elective, and how much time should be dedicated to this topic. Demographic information was collected. The survey remained open for one month and two reminder emails were sent during the midpoint and final week of the data collection period, which occurred in February and March 2012. Descriptive statistics will be used to report responses. Results: Reported outcomes will include information relating to the study objectives. Conclusions: By characterizing pharmacy faculty knowledge and perceptions of PCMH in pharmacy education, it is anticipated that opportunities for faculty and student education can be identified.

Acknowledgements: Kyle Porter (Biostatistician)

DRUG SHORTAGES: MANAGEMENT AND RESPONSE IN HEALTH-SYSTEM PHARMACY

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Background/Introduction: The importance of managing drug shortages has increased over the past decade as the number of drug shortages has also increased. As a result, there is an increased burden on health-systems, and changes to clinical practice and inventory management have been occurred. The purpose of this study is to examine the relationship between hospitals' perceived success at drug shortage management with the level of multidisciplinary and executive involvement in drug shortage management, and adherence to American Society of Health-System Pharmacists' (ASHP) shortage management guidelines.
Methods: Prior to commencement, this study was determined to be exempt from review by the OhioHealth and Ohio State IRBs. Using the Qualtrics™ online survey tool, a survey was emailed to 555 directors of pharmacy at non-federal, acute care sites identified in the publicly available ASHP online residency directory. This survey assessed the three main study variables, and collected demographic information about the respondent's position and hospital.
Preliminary results: The survey is still open to respondents, so final results are pending. A total of 177 respondents completed the survey as of April 17, 2012, yielding a response rate of 32%. 61% of respondents agreed with the statement that their institution successfully managed drug shortages, and only 27% strongly agreed. Patient care threat assessments occurred more often than financial threat assessments. 95% of respondents said that they engage in stockpiling of medications, a practice not recommended by ASHP guidelines. Respondents reported high frequency of consultation with medical and pharmacy staff, but lower frequency of consultation with nursing, hospital executives, and risk management.
Discussion: Final results are pending close of survey and full statistical analysis. These results will help evaluate the impact of ASHP guideline utilization and multidisciplinary and executive participation on perceived shortage management success.

MEDICATION EVENT HUDDLES: EFFECT OF AN ELECTRONIC DATABASE ON INTERVENTION FOLLOW-UP IN A PEDIATRIC HOSPITAL

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Purpose: To determine the impact of an electronic database on the percent of interventions completed following medication event huddles.

Methods: An audit was conducted at a free-standing academic pediatric hospital using retrospective data from the medication event huddle database. Intervention follow-up from medication event huddles was assessed between the time periods of March 1, 2010, through July 1, 2011. Data collection included the original event report summary, names of medications, staff members involved, location of the event, date of occurrence, type of intervention, and the time to completion of each intervention following a medication event huddle. Data were entered into Microsoft Excel® spreadsheet to allow for descriptive statistical analysis. An electronic database was created to eliminate the use of multiple systems for huddle management, allow for documentation of medication event huddles, and generate automatic reminders to individuals involved in the huddle/intervention follow-up. The primary outcome assessed was the percent change in completion of intervention follow-up after implementation of an electronic database. Secondary outcomes included categorization of interventions from the medication event huddles.

Results: The baseline results of this study indicate only 31% of interventions from medication event huddles are documented as being completed. The percentage of interventions completed or in progress, but not documented as such is unknown. Process changes, education, and order improvements are the most frequent categories of huddle interventions. Implementation of a user friendly electronic database could facilitate documentation and management of interventions and ultimately increase patient safety. Database build to be complete by March 1, 2012.

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PATIENT-CENTERED CARE AT A GENERAL INTERNAL MEDICINE PATIENT-CENTERED MEDICAL HOME

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Purpose: To 1) Determine patient perceptions of the degree of patient-centeredness of visits with a pharmacist, internal medicine resident, attending physician, nurse practitioner, social worker, or any combination of the above at a tier 3 General Internal Medicine (GIM) Patient-Centered Medical Home (PCMH) and 2) Examine potential differences of patient-centeredness perceptions based on healthcare provider(s) providing care during each visit.

Methods: A convenience sample will be used to recruit GIM patients age 18 years and older. Data will be collected via a one-time electronic 21-item Consultation Care Measure (CCM) questionnaire at the end of a GIM visit with one or more of the specified healthcare practitioners. Reported data will include a total CCM patient-centeredness score, as well as scores on each of 5 CCM patient-centeredness subscales. Demographics, the amount of time subjects spent with healthcare providers, the amount of time spent waiting, and the length of time each subject has been followed at the PCMH will also be collected. Comparison data analysis will take place to examine correlations between the above items and subject perceptions.

Results: With at least 50 responses in the pharmacist, attending physician, and diabetes clinic practitioner groups, the study will have 80% power to detect a 10% difference in CCM scores between provider types. At the time of abstract submission, a total of 151 questionnaire responses have been collected.

Conclusions: We postulate that results will be used to guide future initiatives implemented to improve patient-centered care, and will support new team-based healthcare models.

PHARMACY RESIDENTS' PURSUIT OF ACADEMIC POSITIONS

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Purpose: Determine the percentage of pharmacy residents that accept an academic position at the end of residency, identify factors influencing residents' decision to pursue/not pursue academia, compare perceived characteristics of the ideal position early in residency versus characteristics of positions accepted upon completion.
Methods: Study includes PGY-1 and PGY-2 pharmacy residents, and consists of an electronic pre-/post-survey with matched responses. Survey invitations were disseminated via residency directors in October 2011; residents who provided an email address will receive the May 2012 follow-up survey. Job preferences, characteristics of the ideal job, interest in academia, and experience in teaching and research were evaluated in pre-survey. End-of-residency survey will focus on job selection, including applied and accepted positions, with specific questions regarding the pursuit of academic positions and characteristics of positions accepted by residents. Results: Pre-survey had 1002 respondents (approximately 39% response rate), 936 pharmacy residents were included (71.6% PGY-1, 26% PGY-2, 2.3% combined program). 46.4% of residents agreed they were seriously considering a position in academia, 30% were neutral, and 22.8% disagreed. Formal training in teaching was available to 71.9% of residents, while 26.5% had formal training in precepting and 16.4% in research. The top settings where residents wanted to work upon completion of residency were inpatient clinical (68%), academia (40%), and ambulatory care (31%). More PGY-2 residents (59.8%) than PGY-1 residents (30.8%) chose academia as a top two career option ($p<0.001$). Academia was more likely a top choice for ambulatory care (55.2%) and specialty inpatient residents (63%) than pharmacy practice (27.7%), managed care (19%), and administrative (33.3%) residents ($p<0.05$ for all comparisons). Top characteristics of the ideal job were collaboration with others (63%), variety of daily activities (46%), and free time for leisure/family (35%). Conclusions: Post-graduate trainees are ideal candidates for faculty recruitment, with many interested in academia. However, many residents likely need additional training for some responsibilities.

Acknowledgements: Kyle Porter, MAS

MEDICATION ERRORS WITH PARENTERAL NUTRITION: IMPACT OF INGREDIENT SHORTAGES

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Background: Ingredient shortages have a significant impact on parenteral nutrition (PN) safety. Due to a lack of appropriate alternatives for PN therapy, the utilization of unfamiliar products or systems has risen and in some instances has led to harmful medication errors. Shortages have affected nearly every component of PN in recent years. The relationship of PN ingredient shortages to harmful medication errors has not been formally evaluated. This study characterizes PN medication errors and correlates them with recent medication shortages, with a particular interest in preventable events with harm (NCC-MERP Index E-I) that occurred as a result of PN ingredient shortage.
Methods: Medication errors involving PN that were reported to the national, anonymous reporting MED-MARX database between May 2009 and April 2011 were reviewed. All errors were categorized by ingredient, node, and severity. The categorization of the reported events was validated by an expert panel. A timeline of PN ingredient shortages was collected, and compared with the PN errors to determine if events could have been directly caused by an ingredient shortage. This information was used to determine the prevalence and change in harmful PN events during periods of shortage, determining if a statistically significant difference exists in errors during shortages as compared with a control period (i.e., no shortage).
Results: Parenteral nutrition shortages were associated with thirteen errors; most of these were associated with intravenous fat emulsions. Nineteen errors were associated with patient harm. Errors were primarily associated with ordering, transcribing, and administration nodes.

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EVALUATION OF THE RATES AND CHARACTERISTICS OF ABANDONED PRESCRIPTIONS PRESCRIBED BY FEDERALLY QUALIFIED HEALTH CENTER PROVIDERS AT 340B CONTRACTED COMMUNITY PHARMACIES

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Purpose: Federally Qualified Health Centers (FQHCs) are eligible to participate in the 340B Drug Pricing Program, which helps provide affordable medications to eligible patients. The program allows FQHCs to contract with local community pharmacies. This opportunity places community pharmacists in a unique position to care for underserved patients, including monitoring medication adherence. Medication adherence plays an important role in patients' overall health. Non-adherence, which may be found in the form of prescription abandonment, may lead to increased hospitalizations, health care costs, morbidity and mortality. An abandoned prescription is one that was filled by the pharmacy, but not picked up by a patient. Our focus will be to evaluate and compare the rates and characteristics of abandoned prescriptions prescribed by FQHC providers versus all other non-FQHC providers at select 340B contracted community pharmacies.

Methods: Abandoned prescriptions at four 340B contracted community pharmacies, part of a grocery store-based chain within Ohio, will be identified during the study period. The pharmacy database will be utilized to identify abandoned prescriptions and their characteristics such as whether it was prescribed by a FQHC provider or non-FQHC provider, the amount owed by the patient, and if it is a new or refilled prescription. All prescriptions that are picked up (not abandoned) from the 340B contracted community pharmacies will also be identified and their characteristics will be collected to use as a comparator group. Data will be analyzed once all information is collected.

Preliminary Results: Data collection will occur from February to May 2012. Preliminary results will be presented at The Ohio State University College of Pharmacy Research Day.

Conclusions: Study results will identify potential differences between groups and could provide opportunities to improve prescription abandonment rates in this FQHC patient population.

Zinc Deficiency in the Context of Obesity

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Obesity is a significant health care problem that causes increased morbidity and mortality worldwide. Zinc is known to play an essential role in preserving immune function whereas chronic obesity is associated with immune dysregulation resulting in a low-grade, systemic inflammatory state. Although zinc deficiency and obesity commonly coexist in humans, it is not currently known what role, if any, that zinc plays in the setting of obesity. Based on this, we investigated a mouse model of obesity to determine whether zinc deficiency enhances the development of a chronic inflammatory state. To establish this we investigated obese and control mice that were further subject to zinc-deficient and zinc-sufficient dietary intakes. As expected, mice on high-fat diets gained significantly more weight (42%) when compared to control mice at 10 weeks. Zinc deficient/high-fat fed mice exhibited a similar increase in fat accumulation and composition when compared to the obese control group. The combined zinc deficient/obese diet resulted increased NF-κB activity, a pro-inflammatory transcription factor, and decreased PPAR-γ activity, an anti-inflammatory transcription factor. Importantly, these changes, as determined by target gene activation and a direct activity assay, were most pronounced in obese/zinc deficient mice. We are now examining whether changes in zinc metabolism at the cellular and tissue level modulate the activity of these proteins.
Funding: Intramural competitive support provided by the OSU Food Innovation Center (DLK).

TREATMENT OF AUTOIMMUNITY THROUGH TOLERANCE

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Clinical studies have shown women with multiple sclerosis exhibit fewer to no symptoms during pregnancy but have more frequent and severe symptoms in the first few postpartum months. During pregnancy the body is in what is known as a tolerogenic state, meaning the immune system's response to certain antigens is down-regulated. The aim of this study was to test drugs that mimic this tolerogenic state by decreasing immune responses like nitric oxide release, while increasing proliferation of certain cell subsets, such as FOXP3+ T regulatory cells. RAW 264.7 macrophages were exposed to estradiol, a hormone prevalent during pregnancy, and all-trans retinoic acid, a compound prevalent in the gut and vital during fetal development, to evaluate their efficacy in suppressing an innate immune response. The nitric oxide (NO) production of the macrophages, when stimulated by lipopolysaccharides, was evaluated for both compounds. Our results indicated that NO levels were not altered by these compounds and further analysis will need to be performed using other immune related cells.

PURIFICATION AND IDENTIFICATION OF AN ANTILEISHMANIAL COMPOUND FROM THE ROOTS OF *THALICTRUM RUGOSUM*

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Leishmaniasis is a significant public health concern throughout 88 countries worldwide, currently with approximately 12 million infected individuals.[1] Transmitted by an infected female sandfly vector, protozoan parasites of the genus *Leishmania* cause leishmaniasis via infiltration of tissue macrophages in host cells.[2] Current treatments are known to be accompanied by adverse side effects, ranging from nausea to serious cardiotoxicity.[1] Isolation of endemic populations in developing countries has also stifled funding for and efforts toward the discovery of more effective treatments, which is becoming a growing concern as *Leishmania* species continue to develop increasing drug resistances to the most commonly employed treatments in modern medicine.[1-3] The need for affordable, more effective, and less toxic treatments has led us to screen samples from a natural products library against *L. donovani* promastigotes. Sample tb-00097 displayed antileishmanial activity with IC_{50} = 1.12 µg/mL. This lead was observed to be impure and was purified chromatographically. Finally, the identity of tb-00097 was determined by NMR spectroscopy and mass spectrometry to be thalicthuberine, formerly isolated from the roots of *Thalictrum rugosum*.[4]

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SYNTHESIS AND CHARACTERIZATION OF ETHANOL-DEGRADING ACETALATED DEXTRAN POYLMER AND MICROPARTICLES

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In the field of drug delivery, pH-sensitive polymeric microparticles can be used to release therapeutic payloads slowly in extracellular conditions (pH 7.4) and faster in more acidic areas *in vivo*, such as sites of inflammation, tumors, or intracellular conditions. Our group applies the pH-sensitive polymer acetalated dextran (Ac-DEX), which is a biodegradable polymer with highly tunable degradation kinetics. Ac-DEX has displayed enhanced delivery of vaccine and drug components to immune and other cells, making it an extremely desirable polymer for immune applications. Currently, one of the degradation products of Ac-DEX is methanol, which may cause toxicity issues if applied at high concentrations with repeated dosings. Therefore, in this project we report the first synthesis and characterization of an Ac-DEX analog which instead has an ethanol degradation product; we abbreviate this polymer as Ace-DEX, with the 'e' to indicate an ethanol byproduct. Like Ac-DEX, Ace-DEX microparticles have tunable degradation rates at pH 5 (intracellular). These rates range from hours to several days and are controlled simply by reaction time. Ace-DEX microparticles also showed minimal cytotoxicity compared to commonly-used poly(lactic-*co*-glycolic acid) (PLGA) microparticles when incubated with macrophages. This study aims to pave the way for the use of Ace-DEX micro/nanoparticles in drug delivery and also allow acetalated dextran-type polymers to be used in high volume applications such as multiple dosing and tissue engineering.

ANTIPSYCHOTIC DRUG IMPACT ON DOPAMINERGIC NEURONS

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Antipsychotic drugs are used to treat schizophrenia. These drugs block dopamine D_2 receptors and increase levels of the neurotransmitter dopamine in extracellular signaling space (a measure of rate of dopamine utilization) to a similar extent. However, various antipsychotic drugs differ substantially in the amount of increase elicited in rate of synthesis of new dopamine molecules and in the amount of increase of dopamine's metabolite, DOPAC (another measure of rate of dopamine utilization). Thus, two markers of dopamine utilization show divergent results when analyzing effects of some antipsychotic drugs. The purpose of this study is to explain this divergence. A computational model of dopamine varicosities was used. This model includes all known mechanisms and pathways for dopamine and DOPAC creation, transport, and metabolism. The activity of parameters in the model was varied until model output matched published experimental data. The results suggest that the effect of blocking dopamine D_2 receptors (shared by all antipsychotic drugs) is to increase levels of extracellular dopamine and to produce a small increase in rate of dopamine synthesis and in levels of DOPAC. Thus, these measurements are a valid indicator of rate of dopamine utilization. The larger increases in rate of dopamine synthesis and in levels of DOPAC observed after some drugs were best modeled by an increase in passive diffusion of dopamine from storage vesicles into cytosol. Review of the literature documents that these drugs are all lipophilic weak bases which would be expected to somewhat alkalinize storage vesicles. Rate of passive dopamine efflux is an expected outcome of vesicle alkalization. These findings suggest that the large increases in rate of dopamine synthesis and in DOPAC level observed after some antipsychotic drugs results from physico-chemical properties interactions of the drugs with dopamine storage vesicles rather than from interaction with dopamine D2 receptors.

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DEPLETION OF PIN1 IN MOUSE AORTIC ENDOTHELIAL CELLS INCREASES INDUCTION OF HYPOXIA-INDUCIBLE TRANSCRIPTION FACTORS

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Oxygen is required in order for cells to survive. Consequently, cells have developed mechanisms to adapt to changing oxygen concentrations. Hypoxia Inducible Transcription factors 1 and 2 (HIF-1 and HIF-2) are induced by hypoxia. HIFs are believed to regulate expression of proteins that promote cell survival and function, allowing organisms to adapt to low oxygen. HIFs therefore may be manipulated to protect normal cells from hypoxia and or conceivably suffocate cancerous cells.

Our lab has investigated the regulation of signaling by PIN1, an enzyme that isomerizes phosphorylated serine/threonine-proline motifs in proteins. This activity allows PIN1 to modulate phosphorylation-dependent protein functions. HIF-1 and 2 are regulated by phosphorylation, but it is not yet known whether they are regulated by PIN1.

This question was addressed here. In order to investigate this we exposed mouse aortic endothelial cells, that either contained or lacked PIN1, to 1% or 21% oxygen for 4 hours. Protein was then extracted from the cells and western blotted to analyze for differences in the expression of HIF-1 and 2.

Results. While the HIFs were not induced in endothelial cells containing PIN1 under these conditions, depletion of PIN1 increased the induction of HIF-1 and HIF-2 by hypoxia 7- and 5-fold, respectively.

The results indicate that PIN1 regulates induction of HIFs. Furthermore, they suggest that PIN1 may act on the phospho-serine/threonine-proline motifs in HIF proteins and/or components of the pathways regulating the HIFs in MAEC. Regulation of HIF expression in hypoxia by PIN1 could affect physiological angiogenesis and/or tumor growth.

IMMUNOSTIMULATORY POLYSACCHARIDES AS A BASE MATERIAL FOR POLYMERIC MICROPARTICLES

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The use of polymers to enhance the delivery of vaccines is a growing area of research. Biocompatible polysaccharides such as dextran can be used as base materials to form acetalated polymers, such as acetalated dextran. Acetalated polymers have been shown to have pH-sensitive characteristics ideal for delivery of vaccine elements to immune cells. Microparticles formed from acetalated polysaccharides form vaccines by encapsulating a protein target (an antigen) and an immune danger signal (an adjuvant). Rather than adding an adjuvant to the vaccine system, immunostimulatory polymers could be used in place of adding additional drug. To this end, different polysaccharides are being tested to determine if they are immunostimulatory. The seven different polysaccharides that are being tested are laminarin, zymosan A, inulin, inulin (from dahlia), glucan from euglena, glucan from barley, and curdlan. These polysaccharides have been shown to activate immune cells and therefore are likely to prove to be immunostimulatory. To evaluate these base materials, macrophages were incubated with four different concentrations of each polysaccharide (10 ug/ml, 1ug/ml, 100 ng/ml, or 10 ng/ml). As a positive control, lipopolysaccharide-stimulated (pro-inflammatory signal) macrophages were also studied as well as a negative control without treatment. The nitric oxide concentrations were evaluated in these test groups. Initial results show that laminarin and inulin were shown to be immunostimulatory at 1 ug/ml. Further testing will be done on the other polysaccharides, and as well as laminarin and inulin, to determine the immunostimulatory nature of the polysaccharides. After determining the immunostimulatory nature and examining other properties of the polysaccharides, the polysaccharides can be used as base materials for acetalation to generate a new polymeric vaccine carrier.

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EVALUATING DRUG THERAPY DECISION MAKING IN PATIENTS WITH EPILEPSY

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Background: When epilepsy patients are given advice about changes to their drug regimen, only a portion of them follow it. Decision making ultimately influences adherence and non-adherence is dangerous for patients with epilepsy.
Objective: The objective of this cross-sectional study was to determine why epilepsy patients do or do not follow suggested advice to change their drug therapy.
Methods: Four weeks after their clinic visit, 100 patients were sent a survey asking them about the prescriber-recommended drug regimen changes, whether they followed the advice, and the main reasons for their decisions.
Results: Of the fifty-one responses received, nearly all (94%) reported that they did follow the suggested advice for changes in their drug regimen. Their reasons included the desire to have fewer seizures (46%), less side effects (17%) and "I trust my practitioner" (26%).
Conclusions: Beyond the desire to have less seizures & side effects, patients report "being heard by" and "trust in" their epilepsy specialist as significantly influencing their decision making regarding changes to their drug therapy.

SYNTHESIS OF ALLOSTERIC MODULATORS FOR NICOTINIC ACETYLCHOLINE RECEPTORS

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Nicotinic acetylcholine receptors (nAChR) can be found throughout the human nervous system. The receptors regulate a multitude of functions, including development, inflammation, and movement. They also serve as the receptor site for nicotine, an extremely addictive drug. Novel therapeutic strategies for breaking this addiction involve synthesis of negative allosteric modulators that could deactivate the binding site for nicotine on these receptors. However, because many subtypes of the nAChR exist, it is difficult to target one without affecting others. This study aims to synthesize a series of analogs of compound **16**, an arylsulfonyl piperazine-containing compound that was previously shown to display selectivity for the Hα4β2 nAChR compared to the Hα3β4 nAChR receptor subtype.[1] Synthetic pathways are focused on amide bond formation between substituted arylsulfonyl piperazines and aryl amines. To date, nine derivatives of **16** have been synthesized. Current results confirm the identity of these compounds by ^{1}H, ^{13}C, *m/z*, and elemental analyses. Biological testing of these compounds has, thus far, shown that the analogs retain the potency of **16** for the Hα4β2 nAChR, but have lost selectivity for that receptor subtype. Future work will focus on exploring different hypotheses regarding the basis of **16** receptor subtype selectivity through the synthesis and evaluation of additional analogs.

1. Henderson, B.; Carper, D.; González-Cestari, T.; Yi, B.; Mahasenan, K.; Pavlovicz, R.; Dalefield, M.; Coleman, R.; Li, C.; McKay, D. *J. Med. Chem.* **2011,** *54*, 8681.