Drug Discovery and Development Colloquium 2015

The University of Mississippi
School of Pharmacy
Thad Cochran Research Center
Room 1000
University, MS
June 22-24

http://ualr.edu/bioinformatics/DDDC2015/

2015DDDC@gmail.com

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Drug Discovery and Development Colloquium 2015
PROGRAM
University of Mississippi School of Pharmacy
Monday, June 22, 2015

12:00-5:00 **Registration TCRC Building 1st Floor**
Room 1000 Atrium

1:00-1:30 **Welcome and Opening Remarks**
Dr. Alice Clark, Chancellor of the Office of Research
Walid Alsharif and Rhianna Morgan, Conference Co-Chairs

Keynote Presentation
1:30-2:30 Dr. Richard Lee, St. Jude's Children's Hospital,
Antibacterial Drug Discovery and Development in the Academic Environment

2:30-2:45 **Coffee Break**

First Session:
Session Chair: Walid Alsharif, U. of Mississippi
Gauri Lamture, U. of Arkansas for Medical Sci.

2:45-3:15 Dr. Kenneth J. Sufka, U. of Mississippi, Drug Discovery for Treatment-Resistant Depression: Moving Beyond the Impasse

3:20-3:50 Dr. Bob M. Moore, U. of Tennessee Health Science Center, Cannabinoid Therapeutics in Reverse

3:55-4:10 Osama Alawin, U. of Louisiana at Monroe, Anti-proliferative Effects of ɣ-Tocotrienol are Associated with Lipid Raft Disruption in Breast Cancer Cells that Overexpress HER2

4:15-4:30 Mohamed Jihan, U. of Mississippi, Simplified Analogues of Artemisinin (Qinghaosu)

4:30-7:30 **Poster Session & Reception (heavy hors d'oeuvres)**

Tuesday, June 23, 2015

8:00-12:00 **Registration TCRC Building 1st Floor**
Room 1000 Atrium

8:00-9:00 **Professional Development Session with Dr. Andy Vick and Dr. Robert Bell**
Shaken, Not Stirred: How to Prepare the Future Pharmaceutical Scientist

Keynote Presentation

9:00-10:00 Dr. Michael Owens, U. of Arkansas for Medical Sci., Monoclonal Antibodies and Vaccines for the Treatment of Methamphetamine Abuse—Discovery, Development, and Testing

Second Session:

Session Chair: Rhianna Morgan, U. of Mississippi
Anqi Wan, U. of Arkansas for Medical Sci.

10:00-10:30 Dr. Kevin Freeman, UMMC, The Study of Drugs as Punishers: Theoretical Implications and Clinical Applications

10:30-10:45 **Coffee Break**

10:45-11:15 Dr. Amal Kaddoumi, U. of Louisiana at Monroe, Targeting the Blood-Brain Barrier as a Therapeutic Approach for Alzheimer's Disease

11:20-11:35 Walid Alsharif, U. of Mississippi, Synthesis, Biological Evaluation, and Metabolic Stability Enhancement of the Dual Sigma Receptor Antagonist DAT Inhibitor Agents as Potential Pharmacotherapy for Stimulant Abuse

11:40-11:55 Surendra Jain, U. of Mississippi, Selective Anti-Leishmanial Activity of Bufalin and Proscillaridin A Against Intracellular Amastigotes of *Leishmania Donovani*

12:00-12:30 **Boxed Lunches**

Keynote Presentation

12:30-1:30 Dr. Larry Walker, U. of Mississippi
Botanicals and Experimental Pharmacology: History and New Horizons

Tuesday, June 23, 2015

Third Session:

Session Chair: Kelsey Leucke, U. of Mississippi
Ujwani Nukala, U. of Arkansas for Medical Sci.

1:30-2:00 Dr. Robert Bell, Drug & Biotechnology Development, LLC, The Drug Development Process of a Novel First In Class Protein for the Treatment of Prostate Cancer

2:05-2:35 Dr. Mary-Ann Bjornsti, U. of Alabama at Birmingham, Yeast Phenomics: Lessons in Cancer Therapy

2:35-3:00 **Coffee Break**

3:00-3:15 Eric Bow, U. of Mississippi, Design, Synthesis, and Biological Evaluation of Novel Benzofuran Cannabinoid Ligands

3:20-3:35 Robert Hazlitt, Purdue University, Synthesis of Metabolically Stable Glucoside Derivatives with a Difluoromethylene Glucosidic Linkage

3:40-3:55 Eman Ashour, U. of Mississippi, Influence of Pressurized Carbon Dioxide on Drug Loading of High Melting Point Carbamazepine and Hydroxypropylcellulose Matrices using Hot Melt Extrusion

4:00-5:00 **Panel Discussion**

Biological Targets & Drug Discovery
Panelists: Drs. Christopher McCurdy, Tracy Brooks, Maaike Everts, and Kevin Freeman
Faculty Moderator: Bonnie Avery, U. of Mississippi
Student Moderator: Walid Alsharif, U. of Mississippi

6:00-9:00 **Social Event/Dinner**

Wednesday, June 24, 2015

8:00-9:00 **Professional Development Session & Breakfast**

9:00-10:00 Dr. Mahmoud A. ElSohly, U. of Mississippi

10:00-10:10 **Coffee Break**

Fourth Session:

Session Chair: Tamara King, U. of Mississippi
Kevin Hawk, U. of Arkansas for Medical Sci.

10:10-10:25 Amer Tarawneh, U. of Mississippi, Discovery of Small-Molecule as Mu Opioid Antagonist

10:30-10:45 Alaadin Alayoubi, U. of Tennessee Health Sciences Center, In Vivo Evaluation of Transdermal Iodine Microemulsion for Treating Iodine Deficiency using Sprague Dawley Rats

10:45-11:00 Baher Daihom, U. of Tennessee Health Science Center, Development and Physicochemical Evaluation of Taste Masked Liquid Suspension of Clindamycin using Ion Exchange Resin Complex for Pediatrics

11:05-11:20 Pranapda Aumsuwan, U. of Mississippi, The Steroidal Saponin, Dioscin, Isolated from Wild Yam (*Dioscorea villosa*) Root Extract, has the Potential to Modulate Human Breast Cancer Cell Metastasis *in vitro*

11:20-12:00 **Awards Ceremony & Closing Remarks**

Dr. Stephen Cutler, U. of Mississippi, Chair of Dept. of BioMolecular Sciences

Keynote Speakers

Richard Lee, Ph.D.

Dr. Richard Edward Lee is an Adjunct Professor, at Department of Pharmaceutical Sciences of the University of Tennessee HSC. He is also a member at Department of Chemical Biology and Therapeutics of the St. Jude Children's Research Hospital. Dr. Lee obtained his bachelor of science B.Sc. degree in chemistry and his doctorate degree in organic chemistry from University of Newcastle-upon-Tyne, U.K. From 1993-1996, Dr. Lee conducted a postdoctoral research fellow in biological chemistry at Colorado State University, and for one more year at The University of Oxford. Dr. Lee spent three years at the National Institute of Health as a research fellow in medicinal chemistry.

Dr. Lee is an expert in the development of antimicrobial chemotherapies and medicinal chemistry in the academic setting. He has considerable translational science experience in the antimicrobial medicinal chemistry area, working formerly at the NIH, University of Oxford, University of Tennessee Health Science Center and on the AstraZeneca Infection iMed External Science Advisory Panel. Dr. Lee has been involved in multiple projects in the discovery and development of antimicrobial agents for over 15 years, including many structure based drug design and PK driven projects, which provides him with significant expertise. He is also actively involved in national and international advocacy in the fight against drug resistant infections and the need to develop new antibiotics, as highlighted by his work on the Pew Charitable Trust, Scientific Priorities for Antibiotic Discovery – Challenges and Opportunities, working group.

Michael Owens, Ph.D.

Michael Owens is a Professor of Pharmacology and Toxicology in the College of Medicine at the University for Arkansas for Medical Sciences (UAMS) in Little Rock, AR.

Dr. Owens' research interests are in translational science, antibody-based medications, experimental therapeutics, and drug abuse. He has been continuously funded as a Principal Investigator by the National Institute on Drug Abuse (NIDA) since 1986 and was a recipient of an NIH Research Career Development Award for 10 years. He has mentored 12 PhD or MD/PhD students and five post-doctoral fellows, the majority of whom have had individual doctoral fellowships from NIH. He was mentor for a K08 clinician/scientist award and a K25 award for faculty colleagues.

He has served as a grant reviewer and chairman of advisory committees for various federal research agencies, and expert panels including the NIH Small Business Innovative Research Grants program, NIDA, the NSF, the Office of Naval Technology, and the AAAS. Dr. Owens has served on editorial boards, and as a scientific advisor and consultant for industry, government and private agencies including the National Academy of Science and Institute of Medicine. From 2001-2002 he was the founding director of the Arkansas Biosciences Institute, which was established with Arkansas' funding from the National Tobacco Settlement Act. He is a founder and Chief Scientific Officer of InterveXion Therapeutic LLC, a pharmaceutical company based-on Dr. Owens' monoclonal antibody and vaccine medications. Currently, he has eight patents and over 100 publications.

In recognition of his teaching and mentorship he received the *Chancellor's Distinguished Faculty Teaching Award* at UAMS in 2006. In 2012 he received the *Born Distinguished Lectureship Award* from the School of Pharmacy at the University of Mississippi. In 2013 he was honored as the College of Medicine *Dean's Distinguished Faculty Scholar* at UAMS. In recognition of his research and academic accomplishments at UAMS, he was awarded a *Wilbur D. Mills Endowed Chair* in Alcohol and Drug Abuse Prevention in 2000.

Larry Walker, Ph.D.

Dr. Walker is the Director of the National Center for Natural Products Research at the University of Mississippi. His research interests include renal and cardiovascular pharmacology; development of rapid, high volume in vitro screening techniques for natural products; and evaluation of lead compounds in animal models.

Mahmoud ElSohly, Ph.D.

Dr. Mahmoud ElSohly is President and Laboratory Director of ELI. He serves as Research Professor in the National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, and Professor of Pharmaceutics in the School of Pharmacy at the University of Mississippi. Dr. ElSohly is the director of the Marijuana Project at the University of Mississippi, which is funded by the National Institute on Drug Abuse. Dr. ElSohly received a Ph.D. in Pharmacognosy from the University of Pittsburgh. He is board certified by the American Board of Forensic Medicine (BCFM) and the American College of Forensic Examiners (BCFE). Dr. ElSohly holds more than 30 patents dealing with the processing, testing, and detection of drugs of abuse along with other patents dealing with biologically active natural products and compositions for the treatment of cancer and other in the diagnostics area. He has authored over 250 scholarly articles and more than 200 presentations at scientific meetings of professional societies relative to drug discovery, analysis, and metabolism, and many of his articles deal with forensic issues of drugs of abuse. He is constantly presenting his research findings at national and international scientific conferences. He is a member of many scholarly scientific societies and was recognized by The Scientist (April 17, 1995) and Science Watch (January, 1995) as the second most cited author in forensic sciences in the world for the period 1981-1993. Dr. ElSohly is also recognized in the Journal of Analytical Toxicology (October issue, 2004) as being one of the top ten (3rd and 4th) Most Cited Authors and Most Prolific Authors in the journal between 1981 and 2003.

Featured Speakers

Kenneth Sufka, Ph.D.

Dr. Kenneth Sufka earned his Ph.D. in physiological psychology in 1990 from Iowa State University. He is currently a Professor of Psychology, Pharmacology and Philosophy and Research Professor with the National Center for Natural Products Research here at UM. Dr. Sufka has published over 70 articles and chapters in the areas of chronic pain, stress-related disorders and consciousness. Three 2013 publications led to a US-PTO patent issued last April for a drug-efficacy screening assay for treatment-resistant depression. Dr. Sufka has received numerous awards for teaching, research and service over the years including being named one of 31 CASE-Carnegie US Professors of the Year.

Bob Moore, Ph.D.

Dr. Bob Moore earned his Ph.D. in medicinal chemistry in 1995 at the University of Kansas. He is a Professor of Medicinal Chemistry at the University of Tennessee Health Science Center. Research in Dr. Moore's lab integrates synthetic organic chemistry, computational chemistry and biological assays aimed at developing new chemotherapeutic entities. The current areas of research include (1) development of cannabinoid receptor (CB1 and CB2) agonist and antagonist, (2) development of novel therapies for combat causality care with emphasis on hemorrhagic shock and hemostasis, (3) development of GPRC directed anti-neoplastic agents, and (4) combination drug therapies for the treatment of sepsis, stroke and ischemic brain conditions.

Kevin Freeman, Ph.D.

Dr. Kevin Bryan Freeman is Assistant Professor at Department of Psychiatry and Human Behavior of the University of Mississippi Medical Center. Dr. Kevin Freeman earned a B.A. in Political Science/English from The University of Mississippi, Oxford, MS in 1996, and a B.A. in Psychology from the same institution in 2001. He obtained his Ph.D. in Psychology from American University, Washington, D.C., under the mentorship of Dr. Tony Riley, in 2007, and conducted a postdoctoral fellowship at the University of Mississippi Medical Center, Jackson, MS under the mentorship of Dr. William Woolverton.

Dr. Freeman research interest is to examine the hypothesis that long-term cocaine self-administration leads to chronic neuroinflammation that, in turn, contributes to cognitive and behavior deficits, which perpetuate dysfunctional addictive behavior. Working in this context with nonhuman primates (NHPs), Dr. Freeman expanded his behavioral and pharmacological expertise, using self-administration and two-lever choice procedures to study drugs as both punishers and reinforcers. He also trained and managed the technicians working in Dr. Woolverton's lab, which provided essential preparation for project and laboratory management. Since finishing his postdoc in 2010, he has been the PI on three grants, one intramural (completed), one R03 from NIDA (completed), and one R01 from NIDA (current). Working with these grants has provided him with the experience needed to develop, execute, and effectively budget grant-funded research within a proposed timeframe.

Amal Kaddoumi, Ph.D.

Dr. Amal Khalil Kaddoumi, is an Associate Professor at Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of Louisiana at Monroe. Dr. Amal Kaddoumi received her M.S. and Ph.D. from School of Pharmaceutical Sciences at Nagasaki University, Japan. She conducted postdoctoral research in College of Pharmacy, University of Michigan, and for another year at School of Pharmacy, University of Washington. From 1990-2008 she worked as an Assistant Professor in School of Pharmacy at Petra University, Jordan. Prior to joining University of Louisiana at Monroe in 2007, Dr. Amal Kaddoumi spent one year as Research Assistant at School of Pharmaceutical Sciences, Nagasaki University, Japan.

From 1998-2004 Dr. Amal Kaddoumi awarded a scholarship from The Ministry of Education, Culture, Sports, Science and Technology of Japanese Government, Japan. Also, in 2004 she received outstanding graduate student award from Nagasaki University, Japan. Dr. Amal Kaddoumi has published more than 56 peer reviewed scientific articles. Dr Amal Kaddoumi has been serving as Alzheimer's Association Peer Review member and AAPS Peer Review member since 2007. Dr. Amal Kaddoumi research interest is to investigate the role of membrane transport proteins in determining drugs and endogenous molecules disposition and their role in neurological diseases, mainly Alzheimer's disease. Investigating and understanding transport proteins is fundamental to facilitate therapeutic development and delivery.

Robert Bell, Ph.D.

Dr. Robert Bell is President / Owner of Drug and Biotechnology Development LLC, a consultancy to the pharmaceutical industry and academia for biological, drug and device development. Dr. Bell received his B.S. in Chemistry, M.S. in Food Science and Human Nutrition and Ph.D. in Pharmaceutics from the University of Florida. His employment history includes Carter-Wallace, Inc., AL Pharma, UDL Laboratories, Inc., Somerset Pharmaceuticals, Inc. and Barr Laboratories, Inc. Dr. Bell is an Adjunct Professor of Pharmaceutics, National Advisory Board Member and recipient of the Distinguished Alumnus Award from the College of Pharmacy at the University of Florida and Affiliate Faculty at the College of Pharmacy at Virginia Commonwealth University. Dr. Bell has published and presented extensively, and has been issued six patents. Research interests include pharmaceutical and biomedical analysis, CMC, quality, vaccines, biosimilar proteins, women's health products, oncology therapeutics and green pharmaceutical chemistry initiatives.

Dr. Bell has served in various leadership capacities within the American Association of Pharmaceutical Scientists (AAPS) including Chair of the Analysis and Pharmaceutical Quality (APQ) section, Editorial Advisory Board for the Journal of Pharmaceutical and Biomedical Analysis, reviewer for AAPS PharmSciTech and AAPS Journal, 2006 National Biotechnology Conference Chair, AAPS Executive Council Member-At-Large (2009), and the 2010 Chair of the Americas for the joint Pharmaceutical Sciences World Congress / FIP /AAPS Annual Meeting. Dr. Bell currently chairs the AAPS Blog Committee and blogs on a regular basis.

Dr. Bell is a Member of the Council of Experts, General Chapters-Biological Analysis for United States Pharmacopeia, Editorial Advisory Board Member for the *Journal of Chemical and Pharmaceutical Sciences* and *Enliven: Biosimilars and Bioavailability*, Co-Editor for the book *Poorly Soluble Drugs: Dissolution and Drug Release*. Dr. Bell is a member of the American Society of Clinical Oncology, American Urology Association, American Chemical Society and the American College of Clinical Pharmacology. Dr. Bell participates in the Visiting Scientist Program to universities, colleges and high schools.

Mary-Ann Bjornsti, Ph.D.

Dr. Mary-Ann Bjornsti is Chair of the Department of Pharmacology and Toxicology at the University of Alabama at Birmingham (UAB), and holds the Newman H. Waters Chair of Clinical Pharmacology. She also serves as co-Leader of the Cancer Cell Biology Program and Associate Director for Translational Research in the UAB Comprehensive Cancer Center. She received her PhD from the University of Minnesota in Genetics, followed by a Fogarty Fellowship at the Biozentrum in Basel Switzerland. She did additional post-doctoral training at Harvard University, in the lab of Dr. James C. Wang, and then set up her own lab as an Assistant, then Associate Professor at Thomas Jefferson University in Philadelphia. In 1999, she joined the faculty at St. Jude Children's Research Hospital and was promoted to Full Member. In 2009, she was recruited to UAB as Department Chair. Her long-standing, research interests are in the mechanisms of anti-cancer drug action and in pathways regulating tumor growth and cellular responses to replicative stress. Her lab pioneered the use of the genetically tractable yeast model system to investigate the mechanism of action of DNA topoisomerase I and experimental chemotherapeutics that target this enzyme, with a focus on translating basic mechanisms of chemotherapeutic drug action and cellular pathways that regulate drug responses to human cell lines and mouse models. Her lab actively collaborates with members of the UAB Comprehensive Cancer Center and other UAB researchers to investigate SUMO and mTOR signaling pathways that regulate cellular responses to genotoxic stresses. She is also on the Executive committee for the Alabama Drug Discovery Alliance (ADDA) and has been actively pursuing the development of novel SUMO pathway inhibitors. She serves on several advisory and editorial boards, has organized numerous national and international meetings, and chairs an NIH SBIR/STTR study section. She runs a UAB Translational Concepts meetings and serves on the Executive Committee for the UAB National Clinical Trial Network (NCTN) Lead Academic Participating Site (LAPS) program.

DDDC 2015 Organizing Committee
University of Mississippi

Walid F. Alsharif, B.Pharm. (Co-Chair)

Walid Alsharif received his bachelor of pharmacy (B.Pharm.) degree from Garyounis University in Libya, and joined Dr. Christopher R. McCurdy's research group at the University of Mississippi (Oxford, MS, USA) in 2010 pursing his doctorate studies. His doctoral research focused on the design and synthesis of new ligands for sigma receptors with the goals of developing medications that can treat stimulant abuse and addiction from one project, and identifying novel and selective sigma-2 ligands that can be used as pharmacological tools to isolate and identify sigma-2 receptors to gain greater understanding of their roles in cancer.

Walid Alsharif has received several research awards locally and nationally during the last two years. He received consecutive first place award in 2013 and 2014 in the University of Mississippi's local section of the American Chemistry Society (ACS) Poster Competition. He was recognized with the first place poster award at the 2014 Graduate Student Council (GSC) Graduate Research Forum at the University of Mississippi. He also received a GSC Research Grant Award, and has been recommended for funding of a second grant. The Mississippi Academy of Science (MAS) recognized his work with Honorable Mention distinction for his outstanding manuscript at the 2015 MAS Annual meeting. He also received national recognition from the American Association of Pharmaceutical Scientists when he was awarded the 2014 Graduate Student Research in Drug Discovery and Development Interface Award, in recognition of his excellence in graduate education in the fields of Drug Discovery and Development Interface.

Rhianna K. Morgan, B.A. (Co-Chair)

Rhianna graduated from Hartwick College, Oneonta, New York, with a Bachelors of Arts in Mathematics and a minor in Biology. She is currently a pre-doctoral research assistant within the division of Pharmacology at the University of Mississippi working under the mentorship of Dr. Tracy A. Brooks. Her research is focused on structural elucidation of the G-quadruplex within the promoters of both the Bcl-2 gene and the mid-region of the kRAS gene. She received the Graduate Student Council Grant in the spring of 2014 to identify small molecules that can stabilize the kRAS G-quadruplex which is a potential treatment for pancreatic cancer. She presented this work at the Mississippi Academy of Sciences annual meeting in Hattiesburg, MS and won the first place presentation award. She has also presented at the 2014 Drug Discovery and Development Colloquium in Little Rock, AR, the University of Mississippi, School of Pharmacy poster session, the 31st Southern Biomedical Engineering Conference, the American Association for Cancer Research annual meeting, and the University of Mississippi's Graduate Research Day.

Kelsey G. Luecke, B.A. (Secretary)

Kelsey Luecke graduated from Drury University in Springfield, Missouri, with a Bachelors of Art in Chemistry. She is currently a research assistant in the BioMolecular Sciences Department: Division of Medicinal Chemistry, focusing on the Ph.D. program. Her research is focused on the synthesis of dual acting ligands that are opioid receptor agonists and neuropeptide FF system (NPFF) antagonists.

Tamara I. King, B.S. (Treasurer)

Tamara King is a first year graduate student at the Department of Pharmaceutics. She holds a B.S. in Forensic Chemistry from the University of Mississippi. Tamara's research interests include analytical and forensic chemistry, toxicology, and genetics.

Christopher R. McCurdy, Ph.D. (Faculty Advisor)

Dr. Christopher Robert McCurdy is a Professor of Medicinal Chemistry and Pharmacology at the Department of BioMolecular Sciences of The University of Mississippi. Dr. McCurdy earned a bachelor's degree in pharmacy from Ohio Northern University and a doctorate in medicinal chemistry from the University of Georgia, joined the University of Mississippi faculty in 2001 after a three-year postdoctoral fellowship at the University of Minnesota. He was awarded tenure and promoted to the rank of Associate Professor in 2007. In 2010 he was named co-director of the National Institutes of Health Center for Research Excellence in Natural Products for Neurosciences, based in the School of Pharmacy. He was promoted to full professor of medicinal chemistry and pharmacology in 2013. In 2014, he was named as a Fellow of the American Association of Pharmaceutical Scientists (AAPS). In 2015, Dr. McCurdy was elected to serve as the AAPS Voting Delegate to the United States Pharmacopeial Convention.

He is actively involved with the AAPS and currently serves on the Board of Directors. He chaired the 2013 AAPS Annual Meeting in San Antonio, TX. He has also served AAPS as Chair of the Drug Design and Discovery section.

In 2001 he was awarded the Albert B. Prescott/GlaxoSmithKline Leadership Award from the Pharmacy Leadership and Education Institute. In 2005, he was named the inaugural Dean's Advisory Committee Distinguished Teaching Scholar in the School of Pharmacy and an American Association of Colleges of Pharmacy (AACP) Academic Leadership Fellow. He has been voted Teacher of the Year three times in 2003, 2006, and 2010.

In 2007, he was recognized as the Outstanding Faculty Researcher of the Year in the School of Pharmacy. He serves on the Senior Editorial Advisory Board for Medicinal Chemistry at Synergix Ltd. He also serves as a Senior Editor for Medicinal Chemistry Research and is a member of the editorial boards several journals including the Journal of Medicinal Chemistry, the premier journal in the field. He also serves as a regular reviewer for over 20 journals and the National Institutes of Health (39 review panels). In 2009, he was recognized with the Faculty Service Award from the School of Pharmacy.
In 2010, he was recognized by his colleagues at the University of Mississippi with the Faculty Achievement Award for teaching and scholarship, one of the most prestigious awards from the University.

Dr. McCurdy has published over 90 peer-reviewed papers and has received research funding in excess of $10 Million from the American Association of Colleges of Pharmacy, the National Institutes of Health, the Centers for Disease Control and the National Science Foundation. He has graduated twelve PhD students and mentored several postdoctoral associates. He currently has four graduate students, two postdoctoral fellows and several undergraduate pharmacy and Honor's College students in his laboratory conducting research focused on new treatments for pain, anxiety, depression and drug addiction.

Bonnie A. Avery, Ph.D. (Facuty Advisor)

Dr. Bonnie Avery is an Associate Professor of Pharmaceutics and Drug Delivery, Associate Research Professor in the Research Institute of Pharmaceutical Sciences, and Associate Professor of Environmental Toxicology in the Department of BioMolecular Sciences, at the University of Mississippi, University MS. Dr. Avery received her B.S. in Medical Technology and B.A. in Chemistry from Minot State University, Minot, ND and her Ph.D. in Analytical Chemistry (1994) from the University of North Dakota, Grand Forks, ND. She currently serves as the co-director of the Chemistry and DMPK Core, NIH COBRE CORE-NPN. Her research interests are in the areas of pre-clinical pharmacokinetics, metabolite identification, method development and validation of natural products and their derivatives. Dr. Avery has received grant and contract funding from NIH, CDC, Pharmaceutical Companies, and The University of Mississippi.

Dr. Avery is a member of various professional organizations including the American Association of Pharmaceutical Scientists (AAPS), American Chemical Society (ACS) American Association of Colleges of Pharmacy (AACP), International Narcotics Research Conference (INRC), and Sigma XI. Dr. Avery has held numerous offices in these professional organizations at the national, regional and local level. These offices include AAPS, Southern Regional Discussion Group Chair, ACS Ole Miss Section Chair and Career Program Coordinator, and Sigma Xi President. Dr. Avery is currently serving as the past chair of the Student Postdoc Outreach and Development SPOD committee, chair of the Carrier Services Advisory Committee and a member of the AAPS Foundation Executive Committee. Dr. Avery teaches in the professional and graduate programs in the School of Pharmacy.

University of Arkansas for Medical Sciences
UAMS AAPS Student Chapter

The University of Arkansas for Medical Sciences (UAMS) AAPS Student Chapter was chartered in 2012. It is committed to enhancing the awareness of educational, professional and employment opportunities in pharmaceutical sciences by fostering increased student/post-doctoral fellow participation in AAPS outreach activities and providing opportunities for networking, professional advancement and leadership development.

Paola Ordoñez (Chair)

Paola Ordóñez is a Ph.D. Candidate in Chemistry at University of Arkansas at Little Rock. She received her B.S. degree in Chemical Engineering at Universidad Técnica Particular de Loja (UTPL) and her Masters Degree in Chemistry at UALR. Formerly she was an instructor in Chemistry at UTPL in Ecuador. Currently, Ms. Ordóñez is working in Dr. Cesar Compadre's laboratory at UAMS, and her research is focused on the development of novel anti-leukimc compouds. Ms. Ordóñez is the Chair (2014-2015 of the AAPS UAMS AAPS Student Chapter. Her doctoral research is. She currently has four publications and two patents.

Gauri Lamture (Vice-Chair)

Gauri Lamture is a Ph.D. student in the department of Pharmaceutical Sciences at the University of Arkansas for Medical Sciences. She received her bachelors degree in Pharmacy from the University of Pune, India. Her doctoral research will be focused on the the use of novel sesquiterpene molecules in a pancreatic cancer model. She will also be developing a nanoparticle formulation, with these sesquiterpenes, in order to enhance the delivery of the drug to the tumor. Gauri is the the Vice-Chair (2014-2015) of the UAMS AAPS Student Chapter.

Shraddha Thakkar, Ph.D. (Past Chair)

Dr. Shraddha Thakkar is an ORISE Fellow at the FDA'S National Center for Toxicological Research. She received her M.Sc. degree in Biotechnology from Bangalore University, India and her M.S., and Ph.D. degrees in Bioinformatics from the UALR/UAMS joint bioinformatics program. Dr. Thakkar research interests are on the use of structural and computational techniques for the elucidation of macromolecular mechanisms relevant for drug discovery. Along with her expertise in crystallography Dr. Thakkar has developed strong expertise in macromolecular cloning and expression, and on the use of molecular modeling and virtual screening. She has worked with various biomolecules including anti-meth single- chain fragment variable antibodies, platelets receptors, alpha-tocopherol transfer protein, and the LOX-1 protein. From her research she has six research publications, two USA patent applications and eight research presentations at National meetings. She has received multiple research awards including the Genentech Innovation in Biotechnology award at the 2012 National Biotech Conference, and the Margret C. Etter student lecturer award at the 2012 American Crystallography Association conference. She was also invited to present her research at the 18th Albany Conversation organized by the Journal of Bimolecular Structure and Dynamics. Dr. Thakkar is very involved various leadership activities related to her research career.

She is the founding president of the Regional Student Group - MidSouthernUS of affiliated with the International Society of Computational Biology. She was elected as the 2013 - 2014 Chair, and the 2012 – 2013 Vice-Chair of the UAMS-AAPS Student Chapter. In addition she received excellence in leadership awards from MCBIOS and UALR, including the 2014 Outstanding Ph.D. Graduate Student Award from the George W. Donaghey College of Engineering and Information Technology of UALR. Dr. was elected as Board member of the Midsouth Computational Biology and Bioinformatics Society (MCBIOS) in 2014 and as Chair Elect in 2015.

Brenda Gannon (Chair-Elect)

Brenda Gannon graduated from the University of Arkansas at Little Rock (UALR), receiving three bachelors degrees in Mathematics, Chemistry, and Spanish, respectively, in 2011. In the fall of 2011, she began her studies at the University of Arkansas for Medical Sciences (UAMS) and joined Dr. William Fantegrossi's research group. Her doctoral research focuses on the *in vivo*characterization of "bath salt" constituent 3,4-methylenedioxypyrovalerone (MDPV), using behavioral pharmacology, structure-activity relationships, and assays of neurotoxicity. Her research has been featured on the cover of Neuropsychopharmacology. Brenda Gannon has received several research awards locally and nationally including first place awards at the ASPET Best Abstract Competition at Experimental Biology in 2015 and second place in 2014; first place in the UAMS Seager-Braswell Symposium in 2015 and 2014; and runner-up in the Graduate Student poster competition at the 2012 SCC SOT meeting. Brenda was a member of the Organizational Committee for DDDC2014, which was held in Little Rock, AR. Brenda Gannon passed her candidacy exam in June 2013 and is scheduled to defend her dissertation at the end of this summer.

Mihir Jaiswal (Secretary/Treasurer)

Mihir Jaiswal received his Ph.D. in bioinformatics from University of Arkansas at Little Rock/University of Arkansas for Medical Sciences (UALR/UAMS) joint bioinformatics program. He also holds MS in bioinformatics from UALR/UAMS joint bioinformatics program, a MS(Pharm) in pharmacoinformatics from the National Institute of Pharmaceutical Education and Research (NIPER), SAS nagar, India and a BPharm from Anand Pharmacy College, India. Dr. Jaiswal's doctroak research was focused on the analysis of protein protein interactions using chemical cross-linking mass spectrometry (CXMS) andnovel computational approaches. Dr. Jaiswal is the treasurer and secretary of UAMS AAPS Student Chapter for 2014-15.

Heng Luo (Public Relations/Webmaster)

Heng Luo is a Ph.D. Candidate at University of Arkansas at Little Rock/University of Arkansas for Medical Sciences (UALR/UAMS) joint bioinformatics program. He got his Bachelor degree at Shanghai Jiao Tong University in China and master degree at UALR. He is now also a research participant at National Center for Toxicological Research (NCTR), U. S. Food and Drug Administration (FDA). Mr. Luo's doctoral research focuses on the binding prediction between human leucocyte antigens (HLAs) and peptides via network approaches in order to better understand adverse drug reactions and personalized medicine. Mr. Luo is the Public Relations officer and webmaster of UAMS AAPS Student Chapter in 2015.

Cesar M. Compadre, Ph.D. (Faculty Advisor)

Dr. Cesar Compadre is a Professor at the Department of Pharmaceutical Sciences, University of Arkansas for Medical Sciences Dr. Compadre has extensive research experience, on the development of bioactive compounds based on naturally occurring compounds, and on the use of molecular modeling in drug design and structure-activity studies. He has published over 80 papers and holds over 70 patents related to the development of bioactive compounds. He is also the developer of one FDA approved antimicrobial technology, which is commercially used in about 30% of the poultry plants
in the USA.

Dr. Compadre has a BSPharm degree, and obtained his Ph.D. degree in medicinal chemistry and pharmacognosy, from the University of Illinois at Chicago. He conducted postdoctoral research on structure-activity relationships studies using molecular modeling at the University of Illinois working with Dr. John M. Pezzuto and at Pomona College working with Professor Corwin Hansch. Additionally, he had a sabbatical experience at NASA Ames Research Center in computer modeling. At the University of Arkansas for Medical Sciences he established and directs the molecular modeling facility. He has extensive research collaborations with many scientists locally, nationally and internationally.

PODIUM ABSTRACTS

ANTIPROLIFERATIVE EFFECTS OF γ-TOCOTRIENOL ARE ASSOCIATED WITH LIPID RAFT DISRUPTION IN BREAST CANCER CELLS THAT OVEREXPRESS HER2

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Purpose: HER2 receptor is a member of the human epidermal growth factor receptor family. Abnormal HER2 signaling occurs in approximately 25% of breast cancers. Lipid rafts are specialized domains of the plasma membrane and these detergent-insoluble domains are responsible for conducting the signaling of receptor tyrosine kinases (RTK), such as HER2 receptor. γ-Tocotrienol, a natural form of vitamin E, exhibits its anticancer activity through the inhibition of several tyrosine kinases. This study demonstrates that inhibiting the activation of HER2 receptor by γ-tocotrienol is associated with the disruption of the lipid rafts.

Methods: Human SKBR3 and BT474 mammary tumor cell lines were in maintained serum-free defined media containing 10ng/ml EGF as a mitogen. Cell viability was determined by MTT assay; where as Western blot and immunofluroscence staining were used to determine the effect of the treatments on HER2 receptor and the lipid rafts. HPLC was used to measure the level of the drug in the lipid raft fractions upon discontinues sucrose ultracentrifugation. Lipid rafts fractions were also extracted using triton X-100 assay.

Results: γ-Tocotrienol inhibits human SKBR3 and BT474 mammary tumor cell proliferation, but has no effect on the immortalized human MCF-10 A normal mammary epithelial cell line. Treatment with γ-tocotrienol reduces both the phosphorylation and the dimerization of the HER2 receptor. Phosphorylated HER2 receptor (activated) is found primarily in the lipid raft fractions. Interestingly, the level of γ-tocotrienol is also found mainly in the lipid raft fractions. Pretreatment with γ-tocotrienol blocks the docking of the lipophilic tracer DilC16 within the lipid domains. Finally, disruption of lipid raft integrity by hydroxylpropyl-β-cyclodextrin (HPβCD) blocks the growth inhibitory effects of γ-tocotrienol on SKBR3 and BT474 breast cancer cells.

Conclusion: These findings show that γ-tocotrienol disrupts the integrity of the lipid rafts within the membrane and prevents the dimerization and activation of the HER2 receptor in human breast cancer cells.

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SIMPLIFIED ANALOGUES OF ARTEMISININ (QINGHAOSU)

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Purpose: We set out to repeat the reported synthesis of **2** and conduct derivatization chemistry at C5. In addition, access to C4 via a C5 carbonyl is in principle possible. Because the Mechanism of Action (MOA) appears to be related to a C4 radical by Fe(II)-mediated O1-O2/C3-C4 ring cleavages, logical modifications at C5 would be expected to test the proposed MOA and provide additional SAR to complement known modifications elsewhere in the backbone of the natural product.

Methods: We modified the reported synthesis of **2** due to several non-reproducible, low yielding reactions. We began by reacting ethyl acetoacetate with ethylene glycol and *p*-toluenesulfonic acid to produce 2-carbethoxymethyl-2-methyl-dioxolane **3** which was then reduced to the aldehyde **4** using diisobutylaluminium hydride. The aldehyde underwent anti-selective Aldol condensation with the lithium enolate of cyclohexanone to form the expected alcohol **5**. The labile β -hydroxy group was protected as the tert-butyldimethylsilyl ether **6** which then underwent direct conversion to the spiro-epoxide **7** via the Corey-Chaykovsky reaction. This labile epoxide was then ring opened using ethereal hydrogen peroxide and a molybdenum catalyst affording the hydroperoxide **8**. Finally, simultaneous deprotection, dehydration, desilylation and ring closure were affected readily with *p*-toluenesulfonic acid in moist dichloromethane to give racemic **2** as a stable, crystalline solid.

Results and conclusions: Synthesis of the simplified artemisinin analogue **2** was accomplished as a racemate, although it was shown that conglomerate crystallization of racemic **2** provides a mixture of enantiomeric crystals that can be manually separated into **2a** and **2b**. The reactivity and chemistry of 2 is being explored in order to expand our SAR of artemisinin, and probe proposed MOA.

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Synthesis, Biological Evaluation, and Metabolic Stability Enhancement of the Dual Sigma Receptor Antagonist DAT Inhibitor Agents as Potential Pharmacotherapy for Stimulant Abuse

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Cocaine is a stimulant that causes an increase in dopaminergic neurotransmission accumulation in the brain, particularly in the ventral portion of striatum by its ability to bind with high affinity to the dopamine transporters (DAT). Cocaine also binds to sigma-1 receptors, and several studies have suggested interactions between sigma-1 receptors and dopamine systems in which cocaine appears to act predominantly to produce its behavioral effects. Similar to cocaine, methamphetamine is a psychostimulant, which is considered among the most abused substances worldwide. To date, there are no FDA approved medications to treat the harmful health consequences resulting from either cocaine or methamphetamine abuse. Like cocaine, methamphetamine binds to s□□□□□ receptors with a slight preference for sigma-1 receptors (2 □M) over sigma-2 receptors (47 □M). Therefore, development an effective treatment for cocaine abuse and addiction is necessary to reduce the associated morbidity and mortality, and most importantly, to reduce the impact of these disorders on the individual and society. In the search for an effective drug for the treatment of cocaine abuse and addiction, and based on our previous work on CM699 that showed high affinity for sigma-1 and DAT, and its ability to attenuate the cocaine self-administration. We have found that stimulant self-administration (cocaine or methamphetamine) was blocked by dual inhibition of the DAT and σRs. Furthermore, immunoprecipitattion studies indicated that CM699 blocked the (+)- pentazocine induced dissociation of σRs from BiP, and indication of antagonist effects. However, CM699 had a short half lives in Human and Rat liver microsomes assays (*in vitro*), 12.7 and 4.4 min respectively, and about 4.4 hr in rat *in vivo* assay. Although CM699 had a half-life of 4.4 hr in rat, a compound with utility as a treatment for stimulant abuse will need a longer half-life, achieved either by structural change or by formulation. In this regard, we have decided to make more analogs of CM699 in order to enhance blockade of cocaine self-administration and metabolic stability. The CM699 derivatives were synthesized and their affinities toward sigma receptors and dopamine transporter measured using radioligand binding assays. Among the tested compounds, WA378 had affinities of 5.70, 0.967, and 203 nM at σ1Rs, σ2Rs and DAT, respectively, while CM699 had affinities of 14.0, 2.30 and 318 nM at the same respective sites. These compounds were also screened for their stability in liver microsome assays. All analogs showed superior metabolic stability to CM699. These results suggest that WA378 may be useful as a pharmacological tool in developing new treatments for stimulant abuse (cocaine or methamphetamine), and this novel approach could be a turning point in the development of medications to treat drug addiction.

SELECTIVE ANTILEISHMANIAL ACTIVITY OF BUFALIN AND PROSCILLARIDIN A AGAINST INTRACELLULAR AMASTIGOTES OF *LEISHMANIA DONOVANI*

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Purpose- Visceral leishmaniasis, caused by a protozoan parasite *Leishmania donovani*, is a major global health problem. Toxicity and suboptimal efficacy of current antileishmanial drugs demand discovery of new antileishmanial drugs with better therapeutic profiles. Random screening of a library of plant-fractions identified several fractions with cardiac steroids and as principal antileishmanial constituents. These cardinolides primarily target Na^+/K^+-ATPase and associated antiporter functions. A P-type ion-motive ATPase, with predicted function as a potassium and/or sodium efflux pump, has been identified in *Leishmania donovani* genome. Bufalin and proscillaridine A were selected to probe the essentiality of Na^+/K^+-ATPase and associated functions in *L. donovani*

Methods-. The bufalinolides were tested *in vitro* against different cellular forms of *L. donovani* namely promastigotes, the axenic amastigotes and intracellular amastigotes in THP1 cells. The growth of promastigotes and axenic amastigotes was measured by alamarBlue assay. Growth of intracellular amastigotes in THP1 cells was measured by a parasite rescue-transformation assay. The inhibitors were simultaneously tested against differentiated THP1 cells for cytotoxicity.

Results- Bufalin, a cardiotonic steroid and proscillaridin A, a cardiac glycoside did not show significant activity against *L. donovani* promastigotes and axenic amastigotes. However, both bufanilolides were highly potent inhibitors of growth of intracellular *L. donovani* amastigotes with IC_{50} value in sub-nano molar range. The results indicated that the glycoside moiety was not required for action of the bufanilolide against leishmania amastigotes. Proscillaridin A also showed significant cytotoxicity against differentiated THP1 cells. Potent antileishmanial action of bufalin and proscillaridin A against intracellular leishmania amastigotes was further confirmed by digital image-analysis assay.

Conclusions- Selective and highly potent activity of bufalin and proscillaridin A against intracellular leishmania amastigotes indicate essential role of Na^+/K^+-ATPase functions in survival of the leishmania parasites in extreme acidic environment of phagolysosomal vacuoles in macrophages. Na^+/K^+-ATPase may be a novel molecular target for antileishmanial drug discovery.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL BENZOFURAN CANNABINOID LIGANDS

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Purpose: The cannabinoid receptors, a member of the G-protein coupled receptors (GPCRs) superfamily, have been implicated in numerous human physiological functions and diseases. The receptors, CB1 and CB2, are most concentrated in the central nervous system and immune cells, respectively, and have each become a target of interest. Dual CB1/CB2 agonists such as D9-tetrahydrocannbindol (THC) have demonstrated efficacy in the treatment of nausea, pain, and glaucoma, but suffer from psychotropic effects mediated by CB1, motivating the search for CB2 selective therapeutic agents. Selective modulation of the CB2 receptor has therapeutic potential in many human health issues such as pain, inflammation, and cancer.

Methods: In our efforts to develop CB2 selective ligands, we preliminarily examined structure activity relationships of synthetic and natural terpenoid cannabinoids to design a benzofuranoid aurone-like scaffold. In this work, we describe the synthesis of a lead compound, which showed promising activity and selectivity in computational docking studies.

Results: Our lead compound was found to be a low-micromolar CB2 ligand, with modest selectivity for CB2. Further synthesis of additional analogs led to the discovery of several compounds with nanomolar activity at CB2, with increased selectivity.

Conclusions: This work may lead to the development of a new class of CB2 selective ligands with a novel scaffold.

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SYNTHESIS OF METABOLICALLY STABLE GLUCOSIDE DERIVATIVES WITH A DIFLUOROMETHYLENE GLUCOSIDIC LINKAGE

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Introduction

Strong evidence suggests that oxidative stress is a common feature in many neurodegenerative diseases, such as Alzheimer's, Huntington's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS). Anthocyanins, such as cyanidin-3-O-glucoside, delphinidin-3-O-glucoside, and malvidin-3-O-glucoside are powerful, naturally occurring antioxidants that have shown potential as neuroprotective agents *in vitro*, but are rapidly metabolized primarily through cleavage of their weak glycosyl linkage *in vivo*. Typically, the aglycone has a poor distribution into the central nervous system; therefore, metabolically stable derivatives are needed to investigate the role of antioxidants in neurodegenerative disorders. We envision that bioisosteric replacement of the oxygen of the labile glycosyl linkage with a stable difluoromethylene group will prevent this hydrolysis.

Methods

Of the limited number of synthetic methods available to install a difluoromethylene unit, the most straightforward is the generation of an α,α-difluoroenolate and its subsequent addition to an electrophile. Recently our lab developed a method that utilizes the release of trifluoroacetate from α-keto pentafluoro *gem*-diols as a mild and efficient way to produce α,α-difluoroenolates. The strategy will be used to construct α,α-difluoro glucosides from α,α-difluoroenolates derived from an α-keto pentafluoro *gem*-diol glucose derivative.

Results

Of three different routes investigated, the most efficient yielded the key α-keto pentafluoro *gem*-diol glucose derivative over 9 steps in an overall yield of 11% from glucose. Interestingly, under bromination conditions, the difluoroenolate derived from the α-keto pentafluoro *gem*-diol glucose derivative underwent a halogenation, deprotection, and cyclization reaction to yield a bromo difluoro glucoside.

Conclusions

An efficient method to synthesize an important glucose derived difluoroenolate precursor has been developed. With access to the difluoro enolate derived from glucose, future work will focus on its application to create metabolically stable anthocyanin derivatives with a difluoromethylene glucosidic linkage.

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INFLUENCE OF PRESSURIZED CARBON DIOXIDE ON DRUG LOADING OF HIGH MELTING POINT CARBAMAZEPINE AND HYDROXYPROPYLCELLULOSE MATRICES USING HOT MELT EXTRUSION

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Purpose
The aim of the current research was to investigate the effect of foam like structures produced by pressurized carbon dioxide (P-CO_2) on the drug loading and the dissolution profiles of carbamazepine (CBZ) and low molecular weight hydroxypropylcellulose (HPC) matrices using hot-melt extrusion techniques.
Methods
Carbamazepine (20–50% w/w) and Klucel™ ELF HPC were subjected to thermogravimetric analysis (TGA) to determine their stability at extrusion temperatures. Drug and polymer were mixed and the resulting blends were extruded with or without P-CO2 injection using a twin-screw extruder (16 mm Prism EuroLab, Thermo Fisher Scientific) at screw speeds of 100-120 rpm and temperature range 110–130°C. P-CO2 was injected on segment 6 of the extruder barrel. All of the extrudates were milled and sieved through ASTM #35 mesh. Density, surface area (Gemini VII, Micromeritics), porosity and drug release profiles of the milled extrudates were evaluated to understand the effect of P-CO2 on the hot melt extrudates. DSC and SEM were used to evaluate the physical state of carbamazepine in the extrudates.
Results
TGA data indicated that all physical mixtures were stable under the utilized processing temperatures. Hot-melt extrusion assisted with P-CO2 injection changed the morphology of the extrudates to foam-like structures and increased their drug loading capability. Milled extrudates exhibited lower bulk density, higher surface area and porosity and also demonstrated enhanced drug release compared to the extrudates processed without P-CO2.
Conclusion
Carbamazepine polymeric dispersions can be prepared by a novel technique of coupling hot melt extrusion with P-CO2 injection, which enabled increased drug loading, surface area, and porosity. Furthermore, optimized drug- release profiles utilizing HPC as a polymeric matrix were attained.

List of funding sources
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2. The Pii Center for Pharmaceutical Technology.

DISCOVERY OF SAMLL-MOLECULE AS MU OPIOID ANTAGONIST

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With the increase in the use and abuse of opioid drugs have come an increase in the number of deaths from opioid drug overdose, including a 91% US-increase related with opioid analgesics during the period between 1999 to 2002 [1, 2]. Opioid abuse also contributes to increased healthcare costs, which is estimated at $300 billion/year according to the White House budget office [3]. It has been recognized that the analgesic effects and the unpleasant side effects (such as addiction, respiratory depression, and tolerance) of most therapeutic opioids are primarily due to their interaction with the mu opioid receptor (MOR) [4]. In order to counteract these negative effects, studies are underway to develop MOR antagonists. In addition to treating opioid dependence, MOR antagonists are also used in the treatment of alcoholism, and have the potential for treating a variety of other conditions such as psychosis, obesity, and Parkinson's disease [5]. Until recently, successful receptor-based drug design was extremely difficult, because the interaction between opioid drugs and the receptors were not fully understood at the molecular level. However, since reporting the crystal structure of the opioid receptors [6-8], researchers have been able to take advantage of this knowledge to discover new compounds, which target these receptors and may be useful for pharmacological and medical purposes. The current study aims to design, synthesize and biologically evaluate potential mu receptor antagonists. The preliminary virtual high throughput screening (HTS) has led to the identification of one novel small-molecule mu antagonist. *Acknowledgement: NIH-NIGMS Center of Research Excellence in Natural Product Neuroscience, grant number P20 GM104932.*

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In Vivo Evaluation of Transdermal Iodine Microemulsion for Treating Iodine Deficiency using Sprague Dawley Rats

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Purpose:
To evaluate the transdermal efficiency of an iodide microemulsion in treating iodine deficiency using rats as animal model.

Methods
Animals were fed either iodine deficient diet (20µg/kg iodide) or control diet (200µg/kg iodide) over 17 month period. At month 14, iodide microemulsion was applied topically in iodine deficient group and physiological evaluations of thyroid gland functions were characterized by monitoring the thyroid hormones (T_3, T_4), thyroid stimulating hormone (TSH), iodide ion excretion in urine and the overall rat body weights in both groups. Moreover, morphological evaluations of thyroid gland before and after treatment were performed by ultrasound imaging and through histological assessment.

Results
Prior to microemulsion treatment, the levels of T_3, T_4 and TSH in iodine deficient group were statistically significant as compared to the control group. The levels of T_3 and T_4 increased while TSH level decreased significantly in iodine deficient group within the first four weeks of treatment. After treatment, iodide concentration in urine increased significantly. There was no statistical difference in weight between the two groups. Ultrasound imaging and histological evaluations showed evidence of hyperplasia in iodine deficient group.

Conclusion
Topical iodide microemulsion has shown a promising potential as a novel translational delivery system to treat iodine deficiency.

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DEVELOPMENT AND PHYSICOCHEMICAL EVALUATION OF TASTE MASKED LIQUID SUSPENSION OF CLINDAMYCIN USING ION EXCHANGE RESIN COMPLEX FOR PEDIATRICS.

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Purpose: Clindamycin is an antimicrobial agent that has been widely used against bacterial infections in children. The primary purpose of this work was to mask the intensely bitter taste of clindamycin using cationic ion exchange resin and to develop an oral suspension suitable for pediatric use.

Methods: Several cationic ion exchange resins (Amberlite IRP 64, 69, 69F, 88 and Dowex 50W X2) were evaluated for clindamycin HCl binding using simple aqueous binding approach. Physicochemical characterization studies for the resinate ion complex were performed (i.e. powder flow properties, DSC, TGA, mass spectroscopy, XRPD and both solid and aqueous stability at 25 and 40^{o}C). Moreover, a liquid oral suspension of the taste masked clindamycin resinate complex was developed after screening several excipients for this purpose. The screened excipients were viscosity enhancing, sweetening and flavoring agents. The optimized liquid suspension was further characterized by performing release studies in SGF, SIF, simulated saliva, and by measuring viscosity and sedimentation rate. In addition, stability studies of the optimized formulation was performed at 25 and 40^{o}C, and taste evaluation in adult volunteers was conducted.

Results: The interaction of the ion exchange resins with clindamycin showed greater binding affinity to Amberlite IRP 69. The binding equilibrium was established after 30 minutes. Both DSC and XRPD showed the presence of clindamycin in the amorphous state inside the resinate complex. The optimized suspension formulation showed more than 80% of clindamycin being released within 30 minutes in both SGF and SIF .The resinate powder and the final formulation showed physical and chemical stability at both 25 and 40^{o}C over 4 weeks period. Taste evaluation study showed significant taste improvement.

Conclusions: Taste masked liquid suspension for clindamycin HCl was successfully achieved using the ion exchange resin technique**.**

Funding: *The Center for Pediatric Pharmacokinetics and Therapeutics CPPT at the University of Tennessee*.

THE STEROIDAL SAPONIN, DIOSCIN, ISOLATED FROM WILD YAM (*DIOSCOREA VILLOSA)* ROOT EXTRACT, HAS THE POTENTIAL TO MODULATE HUMAN BREAST CANCER CELL METASTASIS *IN VITRO*

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Purpose: Previously, we have observed that wild yam root extract (WYRE) is able to activate *GATA3* gene in human breast cancer cells targeting epigenome. The present study aims to find out bioactive molecules of WYRE which can modulate *GATA3* gene functions as well as prevent metastasis in human breast cancer cell lines at the molecular level. In this study we have evaluated dioscin (DS), a steroidal saponin extracted from WYRE, for preventing metastatic potential of cancer cells using MDA-MB-231 cells.

Methods: MCF-7 and MDA-MB-231 cells were treated with and without sublethal concentration of DS and used for gene analysis by qPCR, immunoblotting, and immunocytochemistry. Metastatic potential was determined by cellular invasion, migration and wound healing assays.

Results: DS like WYRE is able to reduce cell viability and induce *GATA3* mRNA expression in both MCF-7 and MDA-MB-231 cells in a concentration-dependent manner. The calculated IC_{50} after 72 h exposure is 3.85 μM for MCF-7 cells and 2.07 μM for MDA-MB-231 cells. The cellular morphology in MDA-MB-231 cells is altered by DS from spindle (mesenchymal) to cuboidal (epithelial) shape. Invasion analyses indicate that DS is able to inhibit invasion of MDA-MB-231 cells in vitro. GATA3 protein expression, as evidenced by western blot and immunocytochemistry, was enhanced by DS in MDA-MB-231 cells.. The mRNAs of *ZFPM2*, and *E-Cad* were increased while *VIM* and *MMP9* were decreased by DS (5.76 μM).

Conclusion: These findings indicate that DS has the potential to be used as a breast cancer preventive agent targeting metastasis.

POSTER ABSTRACTS

APPROACHES TO DEVELOPING PERIPHERALLY RESTRICTED OPIOID AGONISTS

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Purpose:
Salvinorin A is a potent and selective kappa opioid receptor (KOR) agonist isolated from the leaves of the perceptiotropic mint Salvia divinorum. Recent research has shown that incorporating aromatic moieties at the 22-position will induce mu opioid receptor (MOR) affinity while retaining KOR affinity. By utilizing metabolically labile linkages between the 2-position, which is essential for bioactivity, and the 22-position there is the potential to create compounds that are peripherally restricted to limit CNS involvement.

Methods:
A series of Michael acceptor-type salvinorin A analogues were assessed for binding affinity at the delta (DOR), kappa (KOR), and mu (MOR) opioid receptors. The most active KOR/MOR analogue was assessed in mouse models of gastrointestinal hypermotility, abdominal pain, and CNS-mediated behavioral assays.

Results:.
This generated one compound with high affinity toward KOR and MOR, K_i = 9.6nM and 52nM, respectively. This lead compound displayed significant activity in peripherally mediated pain models and was devoid of CNS-mediated behavioral effects.

Conclusions:
These results indicate that subtle modifications to the C(2)-side chain of salvinorin A can influence a marked effect on KOR/MOR affinity. Ultimately, this information will be used to improve the rational design and development of peripherally restricted chemotherapeutics.

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THE EFFECT OF MAZ ON KRAS EXPRESSION: A ROLE FOR G-QUADRUPLEX

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Purpose: kRAS is a GTP/GDP binding protein with intrinsic GTPase activity. It affects normal cell proliferation, division, and apoptosis. kRAS is mutated in >30% of all cancers, particularly in 60-90% of pancreatic cancers. Mutated kRAS leads to continuous activity and uncontrolled proliferation. The kRAS promoter contains three distinct G-rich sections – termed the near, mid, and far regions – each capable of forming non-B-DNA conformations called G-quadruplexes. MAZ is a transcription factor suggested to bind the kRAS promoter near region and modulate transcription. However, it is not clear that this is the primary binding region for MAZ, to what DNA structure it is binding, or the biological outcome of this MAZ:kRAS promoter interaction. Our purpose was to evaluate the function and binding interactions of the transcription factor MAZ on kRAS promoter.

Methods: The pancreatic cancer cell lines Capan-1, MiaPaCa-2, Panc-1, and BxPc3 were transfected with various amounts of a MAZ expression plasmid. 48 hr later, cells were harvested, lysed, and MAZ and kRAS mRNA expression were monitored by qPCR. HEK-293 cells were transfected with MAZ and a kRAS promoter-driven luciferase vector to assess the MAZ:kRAS interaction in an isolated system.

Results: In a study of the kRAS promoter using a series of luciferase plasmids, MAZ expression led to a concentration-dependent decrease in promoter activity. In the context of a more multifaceted intracellular mileau as found in the pancreatic cancer cell lines the MAZ overexpression does not alter kRAS transcription until 2000 ng of plasmid is transfected.

Conclusions: MAZ silences kRAS promoter activity in an isolated system, but not in the pancreatic cancer cell lines. Further investigation will determine the kRAS promoter region and structural conformation of DNA (single-stranded, double-stranded, or G4-DNA) to which MAZ is binding and characterize the best molecular target for further drug discover efforts.

Department of Defense research grant.

PROTECTIVE ROLE OF NRH: QUINONE REDUCTASE 2 (NQO2) IN PRIMAQUINE INDUCED HEMOLYTIC TOXICITY

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Purpose- 8-Aminoquinoline antimalarials (8-AQs), including primaquine (PQ), have limited utility due to hemolytic toxicity in Glucose 6-phosphate dehydrogenase deficient (G6PDd) populations. NRH: QUINONE REDUCTASE 2 (NQO2), catalyzes mandatory two-electron reduction of quinones to hydroquinones. Human erythrocytic NQO2 is the only protein target identified for PQ and seems to be a detoxification enzyme for toxic PQ metabolites. The purpose of the study was to investigate the role of NQO2 in hemolytic response of 5, 6-orthoquinone (5, 6-OQPQ), a potential hemotoxic metabolite of PQ

Methods- The normal and G6PDd human erythrocytes were exposed to different concentrations of 5, 6-OQPQ. Methemoglobin accumulation, oxidative stress and depletion of reduced glutathione (GSH) were measured as the biochemical markers for hemotoxic response. The assays were performed in 96 or 384 microplates. To investigate the role of NQO2 in hemotoxic response of 5, 6-OQPQ, the erythrocytes were co-treated with the metabolite and the NQO2 inhibitors namely, melatonin (Mel), resveratrol (Res) and quercetin (Quer).

Result- The hemotoxic action of 5, 6-OQPQ was confirmed with a concentration-dependent increased in methemoglobin levels and generation of oxidative stress in normal and G6PDd erythrocytes. The GSH levels were depleted in G6PDd erythrocytes only. Mel and Quer synergistically increased 5, 6-OQPQ induced methemoglobin accumulation and oxidative stress generation in normal and G6PDd erythrocytes and increase in GSH depletion in G6PDd erythrocytes. Whereas, Res potentiated 5, 6-OQPQ-induced methemoglobin accumulation and GSH depletion, but decreased oxidative stress in normal and G6PDd human erythrocytes, predictably due to strong antioxidant property of Res.

Conclusions - The results confirm hemotoxic property of 5, 6-OQPQ and also indicate that NQO2 might provide a protective cover to the erythrocytes against hemolytic toxicity of phenolic and quinone PQ metabolites. The results partly explain the mechanism of PQ-induced hemolytic toxicity. The knowledge may be useful for development of safer 8-AQ antimalarial drugs.

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A COMPETITIVE MOLECULAR DOCKING APPROACH FOR PREDICTING ESTROGEN RECEPTOR AGONISTS AND ANTAGONISTS

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Purpose: Molecular docking is a well-established molecular modeling technique commonly used in ligand screening and drug design. However, due to high computational costs, fully flexible docking remains impractical. In light of this, rigid docking and limited flexible docking become the most commonly practiced methods. The estrogen receptors (ERs) adopt distinctly different conformations upon binding to the agonists and antagonists. Using the ER subtype α agonist and antagonist conformations, we designed an *in silico* approach that more closely mimics the biological process, and used it to differentiate the agonist versus antagonist status of potential binders.

Methods: The ability of this approach was first evaluated using true agonists and antagonists extracted from the crystal structures available in the protein data bank (PDB), and then further validated using a larger set of ligands from the literature. The usefulness of the approach was demonstrated with enrichment analysis in data sets with a large number of decoy ligands.

Results: The performance of individual agonist and antagonist docking conformations were found comparable to similar models in the literature. When combined in a competitive docking approach, they provided the ability to discriminate agonists from antagonists with good accuracy, as well as the ability to efficiently select true agonists and antagonists from decoys during enrichment analysis.

Conclusions: This approach offers potential applications not only in drug discovery projects in the pharmaceutical industry but also in the screening of potential endocrine disrupting compounds (EDCs) by regulatory authorities to perform risk assessments on potential EDCs.

Hui Wen Ng is grateful for the support provided by the Research Participation Program at the National Center for Toxicological Research administered by the Oak Ridge Institute for Science and Education.

TARGETING THE KRAS G-QUADRUPLEX AS A NOVEL THERAPEUTIC APPROACH FOR PANCREATIC CANCER

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Purpose:

Pancreatic cancer rates have increased over the past decade. Several risk factors lead to a lifetime risk of acquiring this malignant disease. A predominant factor is genetics as over 60% of pancreatic cancers harbor mutations within the kRAS oncogene. Mutant kRAS results in a constitutively active RAS protein that promotes downstream signaling enabling continuous cell proliferation to occur. This study focuses on the formation of secondary DNA structures within the promoter region of the kRAS oncogene and the search to identify selective stabilizing agents. The kRAS promoter has guanine-rich regions capable of forming higher order non-B-DNA structures, G-quadruplexes (G4s). These important structures have transcriptional silencing potential especially in the presence of selective G4-stabilizing molecules. Our central focus is on elucidating the structure of the G4 within the kRAS promoter and to find selective stabilizing molecules to strengthen transcriptional silencing.

Methods:

For structure determination, electromobility shift assays help differentiate intermolecular and intramolecular structures, and identify the number of isoforms present while DMS footprinting allows for the identification of which guanine residues participate in the structures development. Over 1,600 compounds have been screened by FRET melt and promoter activity was examined by luciferase.

Results:

Multiple intramolecular G4s form within the mid-region of the kRAS promoter, existing in equilibrium. Varying physiological conditions (cations, water content) impacts these formations and a tetra-stacked predominant structure has previously been suggested. We have found that the major G4 has a mixed tri-stacked configuration. NSC-317605 selectively stabilizes this structure and suppresses promoter activity.

Conclusions:

This work emphasizes the potential of the G4 within the kRAS promoter as a novel therapeutic target for pancreatic cancer. Elucidation of the mid-G4 will potentiate further identification of small G4-stabilizing molecules that mediate transcriptional down-regulation and targeted cell kill. Upon pharmacophore validation, in vivo studies with Zebrafish and/or mice would be performed.

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A NOVEL α9α10 ANTAGONIST ZZ204G SHOWS ANALGESIC EFFECT IN RATS

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Purpose: Pain is a global public health priority; more than 20% of adults worldwide suffer from pain. Although there are many analgesics on the market (opioids, NSAIDs, etc.), the treatment of pain remains a vexing problem. Recent studies have led to the discovery of non-peptide antagonists of α9α10 nicotinic acetylcholine receptors (nAChRs) as a novel class of safe and powerful analgesic compounds. However more research is needed to determine the mechanism of action and the types of pain that is responsive to these compounds.

Methods: In this study, a small non-peptide α9α10 antagonist, ZZ204G (a *tetrakis*-quaternary ammonium analog), was selected and synthesized. Nociception assays were used to test the antinociceptive efficacy of ZZ204G and morphine, including hot water tail flick latency (TFL), hind limb paw withdrawal hot plate threshold (HPT), paw pressure threshold (PPT) and pinprick sensitivity threshold (PST) tests.

Results: Results showed that ZZ204G has a long lasting analgesic effect with a quick onset in tests for superficial burning (HPT and TFL) and mechanical pricking pain (PST). The effect of ZZ204G was dose-dependent in three assays (TFL, HPT and PST), with ED_{50} values of 190.5 ± 18.8 μg/kg (TFL), 25.5 ± 9.1 μg/kg (HPT) and 167.8 ± 79.9 μg/kg (PST), respectively. However, only weak analgesic activity was observed in the PPT test, which demonstrated that ZZ204G is less effective for deep tissue (muscle and ligaments) pain. Compared to morphine (an opioid), ZZ204G showed higher potency and longer duration of action in TFL, HPT and PST tests.

Conclusions: The non-peptide α9α10 nAChRs antagonist ZZ204G increases the pain threshold in rats, and is a powerful analgesic for treatment of evoked burning and pricking pain.

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INFLUENCE OF DEGASSING ON HOT MELT EXTRUSION PROCESSING

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Purpose: The aim of this study was to evaluate the influence of a degassing step during hot melt extrusion (HME) processing on the physical-mechanical properties of drug-incorporated extrudates.

Methods: Carbamazepine (CBZ) was selected as a model water insoluble drug and Kollidon® 17 PF (Polyvinylpyrrolidone) was used as the polymeric carrier. The drug and polymer were blended and subsequently melt extruded using a twin-screw extruder (16 mm Prism EuroLab, ThermoFisher Scientific). The vent port was used for an in-line degassing during the processing. Differential scanning calorimetry (DSC) was performed to confirm miscibility and morphology of the drug and polymer. Residual moisture was measured by a halogen moisture analyzer balance (MB45 moisture analyzer, Ohaus, USA). In vitro release studies were performed using a USP Type-II dissolution apparatus (Hanson SR8-plus™).

Results: Thermogravimetric and DSC data confirmed the thermal stability and amorphous state of all the extrudates. The moisture content of fresh extruded samples was decreased from 6.2% to 0.7% when degassing vent ports were applied. Furthermore, drug content increased after employing the degassing port (from 91.4% to 99.1%). Improved dissolution profiles were observed for extrudates degassed compared to those without degassing. Additionally, optical microscope photographs of fresh extrudates demonstrated improved homogeneity after the degassing process. Finally, melt extrusion degassing positively affected the final products as well as the processing parameters, such as controlling extrusion pressure and torque values.

Conclusion: Degassing was demonstrated to have significant positive influences on HME process parameters (pressure and torque). Degassing also reduced the residual moisture and enhanced mixing homogeneity within the extruder, which impacted the final product quality attributes.

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SURFACE SIGNATURE ANALYSIS OF THE BINDING PATTERN OF SESQUITERPENE LACTONES TO NF-KB

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Purpose: The sesquiterpene lactones (SLs) are naturally occurring compounds that have shown potent anti-leukemic activity, and have the ability to target leukemic stem and progenitor cells. It has been postulated that, the SLs exert this effect by inhibiting the rapid-acting primary transcription factor NF-κβ by alkylating cysteine-38 in the DNA binding loop and cysteine-120 in the nearby E' region which makes specific interactions with the DNA impossible. NF-κβ is a heterodimer complex of p50 and p65 subunits that interact with the DNA, regulating the expression of several genes. The aim of this study is to study the binding pattern of sesquiterpene lactones to NF-κβ.

Methods: For the drug-receptor interactions apart from geometrical complementarity, it also requires matching interactions between the drug and the receptor. In an effort to study this complementarity, we performed the surface signature analysis of the SLs and around the Cysteine-38 of NF-κβ chain A. We used MOLCAD program to construct the surface of the ligands and the receptor site.

Results: Electrostatic surface signature analysis demonstrated that the Cysteine-38 residue provides an electron rich region for nucleophile interaction of SLs with NF-κβ and the lipophilic surface signature analysis of NF-κβ active site showed that tyrosine-36 and Cysteine-38 residues are providing a lipophilic region for hydrophobic interaction of SLs with NF-κβ.

Conclusions: This study shows that NF-κβ and the SLs have matching lipophilic and electrostatic surface signatures, i.e. a strong lipophilic surface, and a strong electron rich area. Thus, these characteristic surface patterns would explain why the various types of substantially different SLs interact with NF-κβ. These findings could be also used to identify additional naturally occurring compounds with potential anti-leukemia activity and to guide synthetic approaches to develop more potent or specific compounds.

TERATOGENIC POTENTIAL OF 4-*O*-METHYLHONOKIOL IN JAPANESE MEDAKA (*Oryzias latipes*) EMBRYOGENESIS

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The present study was designed to evaluate the teratogenic effects of 4-*O*-Methylhonokiol (4-*O*-MH), a phenolic compound, isolated from the seeds of *Magnolia grandiflora*, using Japanese medaka embryos as the model. Fertilized medaka eggs (Iwamatsu stage 10) were exposed to 1 μM 4-*O*-MH either for 48 h or for 6 days and used for evaluation of cardiovascular parameters such as heart beats, vessel circulation, and thrombus formation. It was observed that the heart beats in 3 dpf were significantly reduced in the embryos exposed 4-*O*-MH. If the 4-*O*-MH was removed from the medium after 48 hours and maintained in hatching solution for rest of the developmental period, the heart beats of embryos were able to get back to normal. However, maintenance of the embryos with 1 μM 4-*O*-MH until 6 dpf showed significant lower heart beats than the corresponding controls. Moreover, the onset of vessel circulation was delayed in the embryos exposed to 4-*O*-MH and occasional thrombi were seen in these embryos. These preliminary data indicate that 4-*O*-MH might be a week teratogen and its continuous presence in the media affects embryo development.

Funding Source: Internal funding

IN VITRO AND IN VIVO EFFICACY STUDIES WITH PARTHENOLIDE AGAINST HEPATOCELLULAR CANCER

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Purpose: To investigate the safety and efficacy of transarterial chemoembolization (TACE) with parthenolide (PTL) and ethiodized oil (Lipiodol) in a rat Walker 256 cell hepatocellular carcinoma (HCC) model.

Methods: PTL cytotoxicity for Walker 256 cells was determined using cell proliferation assays and the colony formation assay (CFA). Rat liver tumors were produced by inoculating Walker 256 cells into the left lobe of the liver of male Wistar rats. Tumor embolization (via the proper hepatic artery) was performed with saline, lipiodol or a PTL/lipiodol solution. The PTL/lipiodol solution (80mM) was delivered at a dosage of 6.7 mg/kg (n=5). In the saline and lipiodol groups (n=5), 0.1 mL of each was delivered identically. Magnetic resonance images (MRI) and bio-luminescence imaging (of luciferase-expressing tumor cells) were used to calculate tumor growth rate.

Results: In vitro results demonstrated that PTL had antiproliferative activity against Walker 256 cells with GI_{50} = 1.5 μM and LD_{50} = 3.0 μM in CFA assay. The mean tumor growth rate was lower in the PTL/lipiodol group than the control group (40% vs 350%); the same was true for the mean bio-luminescence intensity. There was no significant change in mean whole body weight for rats in all 3 groups.

Conclusions: These results suggested that chemoembolization with PTL in lipiodol was a safe and tolerable treatment and was more effective in suppressing the tumor growth.

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THE EFFECTS OF HOT-MELT EXTRUDER SCREW CONFIGURATION ON THE MORPHOLOGY OF ACTIVE PHARMACEUTICAL INGREDIENTS

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Purpose

The objective of this research was investigate the effects of screw configuration on the morphology and distribution of theophylline within a hydroxypropylcellulose matrix processed by twin screw extruder.

Methods

Differential scanning calorimetry and thermogravitmetric analysis (TGA & Diamond DSC) were utilized to confirm the thermal stability of the API, polymer and physical mixtures over the range of temperatures employed during processing. The raw materials were extruded into uniform rods using a co-rotating twin-screw extruder (11 mm Process 11). After achieving a steady processing state, the extruder was stopped, opened and samples were taken directly from the screw elements. Samples that were analyzed by FTIR Chemical Imaging (Cary 660 & 620IR) were smeared onto a glass slide while still molten and analyzed in reflection mode (5.5µm and 11µm spatial resolution). The microscope was equipped with a germanium micro-ATR for enhanced spatial resolution where necessary (1.1µm). The post-extrusion drug content and content uniformity were assessed by taking random samples, dissolving them accordingly and quantifying using a waters HPLC-UV system.

Results

TGA and DSC analysis confirmed the thermal stability of the components and formulations. FTIR chemical imaging analysis was capable of differentiating the physical phase of the API (amorphous vs. crystalline) as well as its spatial distribution within the carrier as a function of the extruder's screw configuration.

Conclusion

A detailed understanding of the effects of a twin-screw extruder's screw configuration on API morphology is critical in terms of producing the type system desired (i.e. amorphous or crystalline dispersion, solid solution, etc.). FTIR chemical imaging is particularly advantageous as it is rapid, precise and doesn't require potentially morphology altering sample preparation techniques such as milling.

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CP 55,940, a full CB receptor agonist, as a comparable substitute for Δ^9-THC

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Marijuana, the common name for *Cannabis Sativa*, became recreationally popular in the 1960s and 1970s. Its popularity prompted law officials to take notice. Its psychoactive effects, as well as the lack of research being conducted on the plant led to the belief that the plant was narcotic-like and lacked any beneficial properties (Perrine, 1996). Due to this, the plant was classified as a scheduled 1 drug by the DEA. CP 55,940 is a known synthetic CB_1 full agonist Martin et al. (1991) was able to determine the efficacy of CP 55,940 in producing effects very similar to those of Δ^9-THC in both in vitro and in vivo studies. Due to Δ^9-THC being classified as a scheduled I drug, it is difficult for research labs to acquire, so the current study seeks to provide information leading to the possible substitution of CP 55,940 for in vivo studies that are designed to evaluate scheduled 1 Δ^9-THC. The results of the current study have confirmed that the previous reports that both Δ^9-THC and CP 55,940 can produce antinociceptive effects, marked decreases in body temperature, reduced locomotor activity, and catalepsy in the mouse tetrad animal model. In addition, the present study confirms that CP 55, 940 is a potent CB_1 agonist as compared to the effects of Δ^9-THC. The present results indicate that the synthetic cannabinoid agonist CP 55,940 is a viable replacement of the scheduled 1 drug Δ^9-THC in the mouse tetrad assay.

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IDENTIFICATION OF NOVEL PHYTOCHEMICAL INHIBITORS OF BOTULINUM NEUROTOXIN A: *IN SILICO* AND *IN VITRO* SCREENING

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Purpose: Botulinum neurotoxins (BoNTs), classified as class A bioterror agents are the most potent known toxins and are the causative agents of botulism. Current, post-exposure treatment using antitoxins is ineffective to treat the already neuron internalized toxin. Our aim is to find novel small-molecule 'phytochemical' inhibitors of BoNT serotype A (BONT A).

Methods: Our approach comprises three stages: selection of plants, *in silico* screening, and validation using bioassays. Selection of plants was made by using 'traditional medicine' based symptoms similar to botulism. Phytochemicals from these plants were screened *in silico* in the six reported BoNT A-inhibitor crystal structures using VSW module in Glide (Schrodinger, LLE). *In silico* results were tested *in vitro* using protease assay against BoNT A Light Chain (LC) and further using the *ex vivo* mouse phrenic nerve-hemidiaphragm *ex vivo* assay (MPNHDA) assay.

Results: Around 850 phytochemicals from these fifteen plants were screened *in silico* in the six reported BoNT A-inhibitor crystal structures. From the *in silico* output, top 50 compounds were selected based on their docking scores, visual inspection and structural similarity. These compounds were screened *in vitro* by HPLC based BoNT LC inhibitor bioassay. Few compounds showed 60 to 70 % inhibition of BoNT A LC when compared to the standards NSC 84094 and CB7967495 (80 to 95%) in the *in vitro* bioassay. Based on the results, seven compounds were further screened using the MPNHDA. At 20 mM, NPC-ACA-3 showed marginal protection by inhibiting the loss of twitch tension in the hemidiaphragm in the presence of BoNT A.

Conclusions: *In silico*, *in vitro* and *in vivo* screening of phytochemicals resulted in the identification of NPC-ACA-3 as a lead. Further structural modification of NPC-ACA-3 and exploiting the unexplored space in the BoNT inhibitor crystal structure could result in a better protection against BoNT A.

FORMULATION OF SOLID SELF MICROEMULSIONS USING HOT MELT EXTRUSION TECHNOLOGY

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Purpose:

To study the role of hot melt extrusion technology in formulation of solid self micro-emulsifying drug delivery system for improving bioavailability of poorly water soluble drug fenofibrate.

Methods:

Different chemical class of lipids were selected for the formulation of solid self microemulsifying drug delivery system (SMEDDS). Solubility studies helped in screening and selecting the lipid for the delivery systems. Polymeric solid surfactants were chosen depending on their HLB and solubilization efficiency.

Poloxamer 188, Poloxamer 337, Poloxamer 407, Gellucire 44/14 were selected as the polymeric surfactant. Drug was dissolved in the lipid and added to the extruder from a reciprocating pump. Twin screw extrusion was carried out in 16 mm Prism EuroLab, ThermoFisher Scientific at 65 °C with two different screw speeds, keeping the drug loading constant.

The self microemulsions formed were evaluated for their physical properties, namely crystallanity using Differential Scanning Calorimetry (DSC) and Dispersion testing. The extrudates were characterized for their drug content and distribution using high pressure liquid chromatography and FT-IR chemical imaging (Agilent Technologies, Cary 660, Santa Clara, CA).

Results:

Solubility of the drug and solidification efficiency was observed to be greater in di-glycerides. DSC analysis indicated the amorphous nature of the extrudates as the drug remained in solublized state in the extrudates. Dispersion testing suggested that the particle size of all microemulsions were in range of 30nm-250nm. FTIR chemical imaging indicated homogenous drug distribution. Screw speed played an important role in the process as low extrusion speed implied greater mixing time for the formulation inside the barrel.

Conclusions:

A continuous manufacturing technique could be employed in the formulation of solid self emulsifying drug delivery system for solubility enhancement of a poorly water soluble drug. Product uniformity and homogeneity was achieved due to hot melt extrusion technology.

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GENE EXPRESSION PROFILING IN MCF-7 AND MDA-MB-231 HUMAN BREAST CANCER CELLS TREATED WITH DIOSCIN

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Purpose: To understand the genetic and epigenetic mechanisms of breast cancer metastasis in human and to discover new possible genetic markers for use in clinical practice.

Methods: We used microarray technology to compare gene expression profiles of non-invasive MCF-7 and invasive MDA-MB-231 cells exposed to dioscin (DS), a steroidal saponin found in wild yam, (*Dioscorea villosa*).

Results: Initially the differential expression of genes (DEG) were identified that followed pathway enrichment analysis (PEA). Of the genes queried on OneArray, we identified 4641 DEG changed between MCF-7 and MDA-MB-231 cells (vehicle-treated). Among these genes, 2439 genes are upregulated and 2002 genes are downregulated. DS exposure (2.03 μM, 72 h) to these cells identified 801 (MCF-7) and 96 (MDA-MB-231) DEG showed significant difference compared to untreated cells ($p<0.05$). Within these gene sets, DS is able to upregulate 395 genes and downregulates 406 genes in MCF-7 and upregulates 36 and downregulates 60 genes in MDA-MB-231 cells. Further comparison of DEG between MCF-7 and MDA-MB-231 cells exposed to DS identified 3626 DEG of which 1700 were upregulated and 1926 genes were down-regulated. From PEA, 12 canonical pathways were significantly altered between these two cell lines (MCF-7 and MDA-MB-231). However, no alteration in any of these pathways was noticed in MCF-7 cell, while in MDA-MB-231 cells only MAPK pathway showed significant alteration. When PEA comparison was made on DS exposed cells, it was observed that only 2 pathways were significantly affected. Further, to identify shared DEG, which are targeted by DS and overlapped in both MCF-7 and MDA-231 cells, we performed intersection analysis (Venn diagram). We found that only 7 DEG are overlapped of which six are reported in the database.

Conclusions: This study highlights the diverse gene networks and pathways through which DS operates to achieve its widespread effects on breast cancer cells.

IRREVERSIBLE ELCTROPORATION CAUSES APOPTOTIC CELL DEATH IN PANC-1 PANCREATIC CANCER CELLS

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Purpose: Irreversible Electroporation (IRE) employs microsecond pulses of high voltage electric current to produce pores in cellular membranes to ablate tumors and other diseased tissues. For most cells, these pores are irreversible and lethal. In surviving cells the pores are large enough and open sufficiently long to allow the entry of macro-molecules. Hence, it is postulated that combining chemotherapeutic drugs with IRE will deliver a higher concentration of drugs into the otherwise surviving cells to increase the number of tumor cells that are killed. Pancreatic ductal adenocarcinoma (PDAC) is fourth leading cause of cancer deaths. Its dismal prognosis, late diagnosis and resistance to drug treatment contribute to the difficulty in its treatment. If IRE is to be used effectively to treat PDAC, alone or combined with chemotherapy it is important to understand whether cells die by apoptosis or necrosis. Such knowledge can be used to select chemotherapeutic drugs that best complement/enhance the IRE-induced mode of death.

Methods: Human pancreatic cancer cells (PANC-1) were irreversibly electroporated using a BTX ECM 830 electroporator and assayed (flow cytometry) for caspase activation (12 hours later) and the ability of Annexin V to bind to the outer cellular membrane (6 h later). Both of these endpoints are indicators of apoptotic cell death.

Results: Cells were electroporated with voltage gradients ranging from 1000 - 3000 V/cm. Most of the cells electroporated with (2500 V/cm or greater died via necrosis, as determined with a flow cytometry Live-Dead assay, administered immediately and 24 hours post IRE. With lower voltage gradients more cells had activated caspases and stained positive for Annexin V two indicators of apoptosis.

Conclusions: IRE at voltage gradients of 2,500 V/cm or greater induces acute membrane damage that causes PANC-1 cells to die via necrosis. Cell death via apoptosis dominates when cells are exposed to lower voltage gradients. From a clinical perspective, apoptotic cell death is preferable to necrosis because the latter leads to more pain, swelling and inflammation in patients. Our results can be used to help translate IRE treatment parameters that induce clinical ablation of pancreatic cancer via apoptotic processes rather than necrosis.

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Development of Selective Irreversible Ligands for Sigma-2 Receptors

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Introduction: Sigma receptors represent a unique class of receptors. There are two sigma receptor subtypes; sigma-1 and sigma-2 receptors. The sigma-1 receptor is well known because of the receptor sequence information and availability of selective sigma-1 ligands; however, not much is known about sigma-2 receptor due to the unavailability of truly selective sigma-2 ligands until the recent evidence that indicates the sigma-2 receptor binding site is localized within the progesterone receptor membrane component 1 (PGRMC1). More interestingly, it has been observed that sigma-2 receptors have a 10-fold higher density in proliferating tumor cells than in quiescent tumor cells, and that sigma-2 receptor agonists are capable of killing tumor cells via apoptotic and non-apoptotic mechanisms. This gives sigma-2 ligands possible application as effective agents for the treatment of cancer, and more importantly, finding selective sigma-2 receptor ligands will help in isolation and characterization of this receptor.

Purpose: To develop novel selective irreversible ligands for the sigma-2 receptor.

Methods: General procedure for synthesis the isothiocyanates: A 1.0 M solution of the corresponding amine (1.0 eq) in dry DCM was cooled down to 0 °C and treated with thiophosegene (3.0 eq). The orange solution was stirred at room temperature till the reaction completion. Solvents were removed in vacuo, and the residue was purified by column chromatography using DCM/MeOH (95/5) eluent to afford pure compounds. All final compounds were tested for their in vitro binding affinity in rat liver membranes at sigma-1 receptors labeled with [3H](+)-pentazocine and at sigma-2 receptors labeled with [3H]DTG (in presence of unlabeled (+)-pentazocine). To determine irreversible binding, membranes were pretreated with the respective isothiocyanates by incubation for 1 hr at room temperature. This was followed by two centrifugal washes, resuspension in buffer, and a 1 hr dissociation period. After buffer resuspension, remaining binding was determined using [3H](+) pentazocine to label sigma-1 receptors or [3H]DTG (in presence of unlabeled (+)-pentazocine) for sigma-2 receptors. Any lost binding was assumed to be due to irreversible binding of these compounds.

Results: We have found that incorporation of an isothiocyanate moiety in our previous selective sigma-2 compounds resulted in the desired electrophilic center that can bind covalently to a nucleophilic residue in the sigma-2 receptor, which in turn will block access of other compounds to the receptor.

Conclusion: We have synthesized and incorporated the isothiocyanate moiety in the heterocyclic aromatic ring of a series of selective sigma-2 ligands that were developed in our laboratory. This has resulted in producing novel selective irreversible sigma-2 ligands with little to no irreversible binding to sigma-1 receptors. The Developed compounds could be useful as pharmacological tools for structural and functional studies of the sigma-2 receptor. In the meantime, further development and characterization of additional irreversible ligands are underway.

COMPUTATIONAL APPROACH TO DESIGN OF PROTEIN KINASE RNA-LIKE ENDOPLASMIC RETICULUM KINASE (PERK) INHIBITORS

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Purpose: Since there are no therapeutically efficacious drugs for Alzheimer's disease (AD), there is an urgent need for disease modifying therapeutics to manage the disease. PERK (protein kinase RNA-like endoplasmic reticulum kinase) has been shown to trigger the excess formation of plaques and of neurofibrillary tangles leading to Alzheimer's-like dementias. In this study, we used pharmacophore modeling to search for new PERK inhibitors.

Methods: We assembled a database from the commercially available ZINC database and then constructed a protein structure-based pharmacophore model using the following procedure. The first step allowed for the preparation of the protein (adjusting the protein structure, adding hydrogens and assigning protonation states). Next, the pharmacophoric regions were recognized as annotation points based on ligand-receptor interactions, and were transformed into pharmacophoric features. The features' radii were adjusted according to the location of amino acid residues. Excluded volumes were determined based on the regions occupied by active site amino acids. Next, we applied ligand-based virtual screening followed by pose fitting methodologies to find potential PERK inhibitor hits. We also implemented water mapping of the PERK active site. For this we used semi-continuum solvation theory, which uses a single explicit probe water and a Poisson-Boltzmann continuum.

Results: More than 40 compounds were predicted to have a high probability to inhibit PERK and were selected for clustering analysis.

Conclusions: A highly selective pharmacophore model was constructed. The poses of ten diverse compounds resembled poses of the native ligand and were selected for biological testing.

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NOVEL SMALL-MOLECULE INHIBITOR OF VEGF IN DIABETIC RETINOPATHY AND AGE-RELATED MACULAR DEGENERATION

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Purpose: Diabetic retinopathy (DR) and age-related macular degeneration (AMD) are among the four most common causes of age-associated blindness in working age and elderly adults, respectively. Vascular endothelial growth factor, VEGF is well-established as a promoter, biomarker, and therapeutic target of neovascularization in both late-stage/exudative DR and AMD. In the present study we targeted VEGF-induced focal adhesion (FA) signaling using a novel small-molecule modulator of paxillin, JP-153.

Methods: Using human primary retinal endothelial cells (RECs) we investigated JP-153 in both proliferation and migration using well characterized cellular assays. Immunoblotting was carried out to identify FA signaling in RECs and its impact by JP-153. Using a topical ophthalmic microemulsion, we administered JP-153 daily in the *in vivo* murine oxygen-induced retinopathy (OIR) neovascularization model.

Results: JP-153 (0.5 μM) significantly inhibited both REC proliferation and migration through decreased phosphorylation of FA proteins paxillin (Y118) and FAK (Y576/577) ($P < 0.001$). In the murine OIR model, JP-153 prevented neovascularization ($P < 0.001$; $n = 12$-14 mice/group) at both 0.5 and 5 mg/kg daily doses; similar to the efficacy purported by the use of anti-VEGF antibodies in the same model. Whole-retina homogenates revealed a dose-dependent reduction in total paxillin levels with JP-153 treatments.

Conclusions: Compound JP-153 afforded sub-micromolar potency *in vitro,* and dose-dependent efficacy *in vivo*. Our data highlight the essential and dynamic role of paxillin in regulating VEGF-induced pathological neovascularization. In summary, we have discovered the first small-molecule modulator of paxillin that is capable of disrupting VEGF-signal transduction during the neovascular stages of DR and AMD – two most common causes of adult blindness.

Assistance for this project was provided by the following: University of Tennessee Research Foundation and the University of Tennessee College of Pharmacy.

MOLECULAR MODELING OF THE ANTI-LEUKEMIC ACTIVITY OF THE SESQUITERPENE LACTONES

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Purpose: Acute myeloid leukemia is a fatal disease, with an overall five-year survival of about 20%. Sesquiterpene lactones (SLs) are a class of natural compounds that have been reported as anti-AML agents. The structural factors responsible for the anticancer activity of SLs have been the subject of numerous studies; however, there is no clear consensus in the relationship between their chemical structure and their anti-leukemic activity.

Methods: We conducted a surface analysis of 10 compounds with reported anti-AML activity. The molecular structures of the compounds were obtained by X-ray crystallography or derived by small modifications of structures with available X-ray structures. Electrostatic and lipophilic surface signatures were established by mapping electrostatic and lipophilic potentials in the water accessible surfaces of the molecules.

Results: Active SLs have a characteristic combination of electrostatic and lipophilic surface signatures absent in inactive compounds; they showed a lipophilic convex surface, and a hydrophilic concave surface in the opposite side of the molecule. In addition, active molecules must have an electron deficient area in the side of the lipophilic surface. Compounds without both surface signatures were inactive.

Conclusions: SLs with anti-leukemic activity have characteristic surface signatures, consisting of a strong electron deficient surface, susceptible to nucleophile attacks, in the middle of a strong lipophilic surface. The implication of this finding is that the SLs receptor should have a complementary a nucleophile, electron rich surface, surrounded by a lipophilic surface.

BIOAVAILABILITY ENHANCEMENT OF VITAMIN E ANALOGUES

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Purpose: There is a growing interest on the use of the tocotrienol components of vitamin E for their radioprotectant, anticancer, and antioxidant activity. Unfortunately, their short elimination half-life limits their potential. Their shorter half-life is due to thei low affinity for α-tocopherol transfer protein (ATTP), the protein responsible for maintaining tocols plasma levels.Tocotrienols, which have less affinity for ATTP than does α-tocopherol, have longer residence time in the liver, putting themat higher risk for metabolism and biliary excretion. The aim of our research is to develop tocotrienols with enhanced binding affinity for ATTP, and therefore better bioavailability.

Methods: Based on structural analysis of ATTP-tocopherol complex we have hypothesized that the flexibility in the tail of tocols is crucial for binding. This hypothesis was tested using comparative molecular dynamics simulations (DS) of the binding of the various tocols to the open form of ATTP. Simulations were conducted by 10 ns at 300K. The DS results were contrasted with the results of experimental determination of the tocol's ATTP binding, measured by thermal stability shift assays. For these assays recombinant ATTP was expressed in E.coli BL21 (pET28) cells with 6His tag on c-terminal and purified with nickel affinity chromatography. Tocols were incubated with purified recombinant ATTP, and heated at stepwise increments of 1°C/min from 25 to 99 °C in presence of SPYRO orange fluorescent dye.

Results: Dynamics simulations showed that when tocotrienols bind to ATTP the protein is not able to adopt the closed conformation. In contrast when tocopherols are in the binding cavity, the protein is capable of adopting the closed conformation. Binding assays correlated very well with the dynamic simulations analyses and suggested that the closed conformation of ATTP is more stable that the open conformation.

Conclusion: Rigidity of the farnesyl side chain of the tocotrienols is a major determinant of their low-binding affinity to ATTP. Newly generated tocotrienol analogues with a flexible tail resulting in better binding affinity with ATTP could have better bioavailability

FIBROBLAST GROWTH FACTOR (FGF) 21 IS A NOVEL TARGET GENE OF GLUCOCORTICOID RECEPTOR

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Fibroblast growth factor (Fgf) 21 is a metabolic regulator that plays an important role in the maintenance of glucose, lipid, and energy homeostasis. Recent studies also suggest that Fgf21 induction can attenuate chemical-induced toxicities, such as of acetaminophen, alcohol and dioxin. Glucocorticoid receptor (GR) is indispensable for cell growth and development, drug metabolism as well as immune response. However, the impact of GR activation on regulation of Fgf21 is unknown. The present study was designed to investigate whether activation of GR by the synthetic glucocorticoid Dexamethasone (DEX), can alter Fgf21 expression.

Our results showed that in mouse liver, both low (2mg/kg) and high (50mg/kg) doses of DEX up-regulated Fgf21 mRNA and protein expression. In addition, DEX induced Fgf21 mRNA and protein expression in both mouse (Hepa1c1c7) and human (Hep3B) hepatoma cells in a concentration- and time-dependent manner. Generally, DEX produces its effects via activation of GR and/or pregnane X receptor (PXR). By using PXR-null mouse model, we showed that 50mg/kg of DEX induced Fgf21 mRNA expression similarly in both wild-type and PXR-null mouse liver, indicating that the induction of Fgf21 by DEX is PXR-independent. The in silico DNA sequence analysis revealed the presence of several putative GR response elements (GREs) in the 3kb promoter of mouse and human Fgf21/FGF21 genes. Further, GR silencing using GR-specific siRNA, attenuated DEX-induced Fgf21 expression in both mouse (Hepa1c1c7) and human (Hep3B) hepatoma cells. Moreover, ChIP assay demonstrated that DEX increased the binding of GR to the promoter region of mouse and human Fgf21 gene.

In summary, activation of GR induced Fgf21 expression in mouse liver as well as in cultured mouse and human hepatocytes.

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COMPARATIVE *IN VITRO* AND *IN VIVO* PHARMACOKINETIC EVALUATION OF NOVEL 4-AMINOQUINOLINE-TETRAZOLE ANTIMALARIALS

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Purpose: S011-0719 and S011-0725 are potent antimalarial and are active against chloroquine-sensitive (3D7) and chloroquine-resistant (K1) strains of *Plasmodium falciparum* both *in vitro* and *in vivo.* Considering the promising antimalarial activity of S011-0719 and S011-0725, *in vitro* and *in vivo* pharmacokinetic studies were performed to establish the ADME profiles in support of their development as candidate drugs.

Methods: Separate HPLC-UV methods for quantification of S011-0719 and S011-0725 in rat serum were developed and validated. To facilitate further pharmacological and pharmaceutical development, red blood cell (RBC) uptake, whole blood partitioning, serum protein binding and stability studies in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and rat liver microsomes were performed. Single dose pharmacokinetic studies after oral (10 mg/kg) and intravenous (10 mg/kg) administration were accomplished in male *Sprague Dawley* rats. The concentration-time data were subjected to noncompartmental approach using Phoenix WinNonlin (version 6.3; Certara Inc, Missouri, USA) to determine the pharmacokinetic parameters of both the compounds.

Results: The stability studies revealed that S011-0725 was stable in both simulated gastrointestinal fluids. At the end of 2 h of incubation in SIF, S011-0719 showed 54% degradation but was found stable in SGF. Microsomal stability studies demonstrated that both the compounds were metabolized by phase I enzymes. At the end of 1 h of incubation in rat liver microsomes, 58.6 and 35.5% of S011-0719 and S011-0725, respectively, remained unchanged. The oral and intravenous pharmacokinetic study of S011-0719 and S011-0725 in the male *Sprague Dawley* rats revealed that the compounds were quickly absorbed, distributed and slowly eliminated from the serum with an elimination half-life of 5.3 and 22.6 h, respectively.

Conclusions: S011-0725 is more appropriate for oral therapy than S011-0719 due to its stability in SIF; 14-times lower clearance, 1.9-times higher AUC and 3.3-times higher MRT after a single oral dose of 10 mg/kg.

ISOLATION OF A NEW PHLOROGLUCINOL DERIVATIVE FROM *HYPERICUM AFRUM*

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The genus *Hypericum* (Hypericaceae) comprises more than 460 species with worldwide distribution. *Hypericum* species have long been used for their biological properties.In fact *H. perforatum*, known commonly as "St John's wort",is used more commonly to treat mild to moderate depression making *H. perforatum* one of the top selling botanical inthe United States and Europe, with $5.6 million in USA-2013 and € 70 million in Germany-2008.

The present work describes the isolation and structural elucidation of the constituents of the chloroformic ($CHCl_3$) and ethyl acetate (EtOAc) extracts of the aerial part of *Hypericum afrum (Lam.).* Species endemic to the Numidia regions and growing in the wetlands in north-eastern Algeria. (P. Quezel, S. Santa, Nouvelle flore de l'Algérie et des Régions Désertiques CNRS, Paris, 1963. P681.).The constituents of the extracts were purified by column chromatography (silica, Sephadex, reverse phase) and analytical and preparative TLC. A new phloroglucinol derivative was isolated from the $CHCl_3$ extract and seven know compounds from the EtOAc extract. The structures of the compounds were elucidatedby extensive 1D and 2D NMR and MS experiments, and by comparison with the data reported in the literature.

The extracts were evaluated for their in vitro binding affinity for human clonedopioids and cannabinoids receptors showing weak binding affinity for both. The EtOAc extract showed promising MAO-A inhibition with an IC_{50} value of3.35 µg/mL. Future bioassay guided fractionation is under way to identify the secondary metabolite responsible for the MAO-A activity.

DEVELOPMENT OF Δ9-TETRAHYDROCANNABINOL PRODRUG WITH IMPROVED IOP LOWERING EFFICACY

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Purpose: In order to improve the ocular bioavailability of Δ9-Tetrahydrocannabinol (THC), a relatively hydrophilic THC prodrug (THC-valine-hemisuccinate; THC-Val-HS) was developed and its intraocular pressure (IOP) lowering activity was evaluated in rabbit α-chymotrypsin induced glaucoma model. The activity was compared to that of THC, WIN 55,212-2 (WIN) and Timolol maleate.

Methods: Nanoemulsion (THC: 0.6%w/v) and micellar (15%w/v of HPβCD and 0.25%w/v of Cremophor®; THC: 0.55%w/v) ophthalmic solutions of THC-Val-HS were tested. Glaucoma was induced in rabbits with a single intravitreal injection of α-chymotrypsin (50µL, 20mg/mL). After IOP stabilized (about 30mmHg), the efficacy studies were initiated. Fifty microlitres of each of the formulations were instilled into the test eye and IOP was measured using a TonoVet® tonometer. The change in IOP from the baseline values (%ΔIOP) obtained with THC-Val-HS was compared with that achieved with THC (nanoemulsion; 0.8%w/v), WIN (nanoemulsion; 0.8%w/v) and Timolol (0.25%w/v). *In vitro* CB1/CB2 receptor binding studies were also carried out to determine the affinity of THC-Val-HS for these receptors. All animal studies were conducted following UM IACUC approved protocols.

Results: At an equivalent dose, THC-Val-HS exhibited greater pharmacological response (%ΔIOP) compared to the parent drug THC. The peak %ΔIOP with the THC-Val-HS nanoemulsion and micellar solutions were about 52% and 62% (90min), respectively. The extent of IOP lowering was similar to WIN; however, with WIN peak %ΔIOP was achieved within 30min. Compared to Timolol, THC-Val-HS produced a greater %ΔIOP but had a shorter duration of activity. *In vitro* receptor binding studies demonstrated that THC-Val-HS did not have any affinity for the CB1/CB2 receptors. This confirmed that the IOP lowering effect was mediated by THC generated from the metabolism of THC-Val-HS in the ocular tissues.

Conclusion: The results demonstrate that hydrophilic prodrug derivatization significantly improves ocular delivery and therapeutic potential of THC.

IN VIVO OCULAR DISPOSITION OF Δ8-TETRAHYDRICANNABINOL SOLID LIPID NANOPARTICLES

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Purpose: Δ8-tetrahydrocannabinol (THC) is a potential candidate for the treatment of glaucoma. The aim of the present study is to evaluate THC solid lipid nanoparticles (SLNs) to improve ocular bioavailability.

Methods: SLNs were prepared using a high-pressure homogenization method. Precirol ATO 5 was melted, and THC was dissolved to obtain a clear lipid phase. An aqueous phase containing 0.25% Poloxamer 188, 0.75% Tween 80 and 2.25% Glycerin (w/v) in distilled water, was heated. The hot aqueous phase was added to the melted lipid phase under stirring. A coarse emulsion was formed using an Ultra-Turrax and then subjected to high-pressure homogenization, resulting in the formation of a hot dispersion which was cooled to form THC-SLNs. In vivo ocular bioavailability of THC was evaluated from the SLNs in anesthetized male New Zealand albino. The formulation was instilled into the cul-de-sac. At the end of one hour, rabbits were euthanized and tissues were analyzed for drug content.

Results: Solution formulation of THC in RMβCD did not produce any detectable THC levels in any of the inner ocular tissues. Mean THC concentrations in the cornea and sclera were 1.2 & 0.44 ug/g of tissue, respectively. SLNs on the other hand, at an equivalent dose, generated significant THC levels in all the ocular tissues tested (aqueous humor: 4.6; iris-ciliary: 0.4; retina choroid: 0.24; cornea: 8.4; sclera: 0.8 ug/g of tissue), except for the vitreous humor. The inability to penetrate into the vitreous humor could be attributed to the high lipophilicity of THC.

Conclusions: The in vivo results demonstrate that SLN formulations could be an effective strategy for ocular delivery of THC. Further studies optimizing the SLN formulations in terms of drug loading and permeation are
currently under investigation.

STEREOSELECTIVE EFFECTS OF ABUSED "BATH SALT" CONSTITUENT 3,4-METHYLENEDIOXYPYROVALERONE (MDPV) IN TWO MURINE BIOASSAYS

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Purpose: In recent years, synthetic analogues of naturally-occurring cathinone have emerged as psychostimulant-like drugs of abuse in commercial "bath salt" preparations. 3,4-methylenedioxypyrovalerone (MDPV) is a common constituent of these illicit products. MDPV is a chiral molecule; however, the relative contribution of each individual enantiomer to CNS effects has not previously been demonstrated.

Methods: To examine the behavioral effects of each enantiomer of MDPV, adult male NIH Swiss mice were trained to discriminate 10 mg/kg cocaine from saline, and the interoceptive effects of a range of substitution doses of racemic MDPV, S(+)-MDPV, and R(-)-MDPV were then assessed. In separate groups of mice, surgically-implanted radiotelemetry probes monitored locomotor responses to various doses of S(+)-MDPV and R(-)-MDPV.

Results: In mice implanted with radiotelemetry probes, locomotor stimulant effects were observed following intraperitoneal (i.p.) injections of 3 and 10 mg/kg S(+)-MDPV and 30 mg/kg R(-)-MDPV, respectively. In these studies, we also found that mice reliably discriminated the cocaine training dose (10 mg/kg) from saline, and that doses of 1mg/kg racemic MDPV, 0.3 mg/kg S(+)-MDPV, and 10 mg/kg R(-)-MDPV all fully substituted for the cocaine training stimulus.

Conclusions: These studies suggest that while both the S(+)- and R(-)- enantiomers of MDPV are bioactive, there are significant potency differences between each enantiomer, with the S(+)-MDPV being more potent than R(-)-MDPV; suggesting the S(+)- enantiomer could be a potential target for MDPV addiction therapy.

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XLPM MAP: A PROTEIN-PROTEIN INTERACTION MAP VIEWER

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X-Linked Peptide Mapping (XLPM) is an algorithm for the analyses of chemical cross-linking mass spectrometry (CXMS) data. XLPM identifies not only the peptide pair interacting with each other but also scores the pair of residues interacting with each other. XLPM map is a viewer of the XLPM results based on tree map visualization. XLPM map shows the protein-protein interactions between two proteins in three levels. The first level shows the highest ranked interactions between digested peptides as a tree map with color intensity reflecting the score. Selecting any of the interaction in the first level opens the second level of visualization. The second level of visualization shows all the precursor ions matching with the selected interaction. It also shows all the details of the spectra. Selecting one of the spectra shows the third level. Third level shows the details scores for interaction between each pair of residues. The visualization within XLPM map makes understanding of the interactions between a protein pair efficient by providing easy access to all levels of information. In future, we will include available protein structures from PDB and map the interactions onto them.

EFFECTS OF DMAPT AND IONIZING RADIATION IN AN ORTHOTOPIC RAT GLIOMA MODEL

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Purpose: Glioblastoma multiforme (GBM) is an aggressive form of brain cancer which is highly resistant to radiotherapy. The sesquiterpene DMAPT, a water soluble parthenolide analogue, has been shown to radiosensitize 9LSF rat glioma cells *in vitro* by inhibiting DNA damage repair. Previous studies using ^{11}C-radiolabeled DMAPT showed drug administered IP localized in the tumors of 9LSF tumor-bearing rats. In this study, we seek to quantify the effect of DMAPT, both alone and in combination with ionizing radiation, in the treatment of orthotopic 9LSF rat glioma *in vivo*.

Methods: 9LSF cells were injected intracranially into male Fischer 344 rats and tumors were allowed to grow to desired volume (~50-75mm^3). Subjects were randomly placed into four groups (control, drug alone, IR alone, or drug + IR). Drug treatment included 5 daily fractions of 100 mg/kg DMAPT administered IP one hour before radiation therapy. Fractionated radiotherapy was administered using a small animal conformal radiation therapy device (1.82 Gy/min) at a dose of 2.5 Gy per day for 5 days. Tumor growth was monitored using MRI and was calculated as fold-increase in volume for 10 days after initiation of treatment.

Results: DMAPT treatment did not significantly alter tumor growth in drug-treated groups versus controls, regardless of radiotherapy. Subjects receiving radiation treatments showed slowed, but continued, tumor growth versus control group.

Conclusions: DMAPT does not represent a viable option, either alone or concurrent to radiotherapy, in the treatment of GBM *in vivo*. Fractionated radiation treatments were able to slow, though not inhibit, tumor growth.

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