Poster #9

Sesquiterpene Lactone Derivatives as Potential Lead Molecules for Treatment of Acute Myelogenous Leukemia

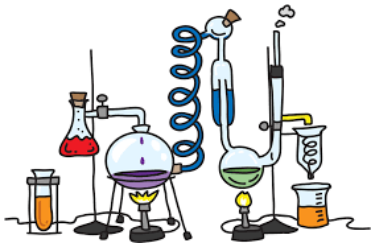
Venumadhav Janganati, Jessica Ponder, Craig T. Jordan and Peter A. Crooks

Acute myelogenous leukemia (AML) is a cancer of the myeloid line of blood cells; it is a clonal malignancy of the hematopoietic system characterized by rapid growth of abnormal white blood cells that accumulate in the bone marrow and restrict the production of normal blood cells. AML is the most common type of leukemia in adults but has the lowest survival rate of all leukemias, accounting for approximately 1.2% of cancer deaths in the United States. Treatments for AML have not substantially changed over the last 30 years, and the incidence of AML is expected to increase as the world population ages. Thus, there is a clear need for new drug therapies to treat this blood-borne cancer.

Our research group has focused on the sesquiterpene lactone, parthenolide (PTL), which we isolated from feverfew (*Tanacetum parthenium*), and which has been identified as an anti-leukemic drug. To improve drug likeness and potency, several parthenolide (PTL) analogs have been as potential clinical candidates. Among these compounds, dimethylaminoparthenolide (DMAPT) was found identified as a promising, orally bioavailable anti-leukemic agent with low toxicity. DMAPT is currently in Phase I clinical studies for evaluation as a treatment for AML and other related leukemias. We are also focusing on derivatives of the structurally related sesquiterpene analog, melampomagnolide B (MMB), a melampolide we have isolated from *Magnolia grandiflora*. MMB can also it can be obtained from chemical modification of the C10 methyl group of PTL. More than 300 analogs of MMB have been prepared. Very recently we designed and synthesized a series of triazole derivatives of MMB by reaction of MMB azide with various acetylenic moieties via “click chemistry” methodologies. These novel compounds exhibited more potent and selective anti-leukemic properties than either PTL or MMB. Among these compounds, the di-trifluoromethyl-phenyl triazole derivative of MMB was identified as a potential anti-leukemic agent that exhibited 32-fold greater potency when compared to PTL, and was considered to be a potential second generation clinical candidate for treatment of AML.

Showcase of Medical Discoveries

Inventors



Wednesday, June 6, 2017
4:30—6:00 p.m.

Winthrop P. Rockefeller Cancer Institute, 10th Floor Rotunda

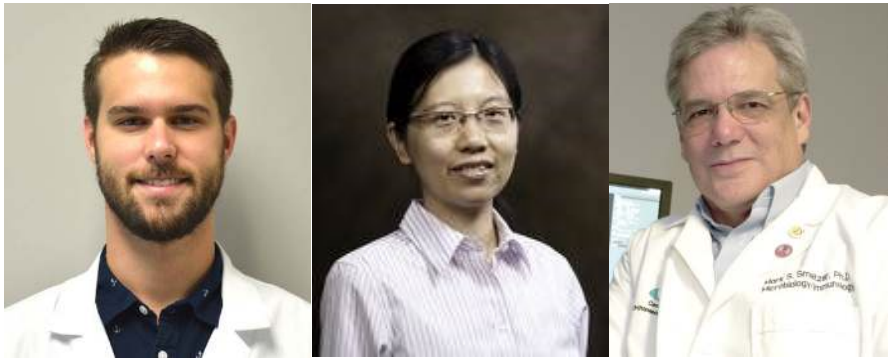
The 18th Showcase of Medical Discoveries will feature UAMS investigators discussing inventions resulting from their research and discoveries. This showcase is open to all interested faculty, students, staff and invited guests. The series’ ongoing goals include, fostering communication and collaboration between investigators and increasing awareness of exciting research in Arkansas.

UAMS College of Medicine

Division of Research

Poster #1

Looking for drugs in all the wrong places: Are antibiotic-loaded gold nanocages the solution for treating Staphylococcus aureus biofilm infections?



Meeker DG, Beenken KE, Mills WB, Nedosekin DA, Chen J, Smeltzer MS

For decades the medical community has relied on antibiotics to control bacterial infections. The ability to do so has been increasingly compromised by the emergence of antibiotic-resistant bacterial strains. This results in the death of over 23,000 people per year in the United States alone. Moreover, many forms of bacterial infection are characterized by formation of a biofilm, which confers a therapeutically-relevant level of intrinsic resistance to all antibiotics. To address these issues, we used *Staphylococcus aureus* as a proof-of-principle "ESKAPE pathogen" to demonstrate that antibiotics can be incorporated into polydopamine-coated gold nanocages, which can then be conjugated to antibodies targeting specific bacterial surface proteins. This allows for selective delivery of antibiotic-loaded nanocages directly to the bacterial cell surface. These gold nanocages can be tuned to absorb light at a wavelength in the near infrared (NIR) range and release this energy as heat, and we have demonstrated that this heat can be used to simultaneously achieve both a lethal photothermal effect and controlled release of antibiotic directly at the surface of the offending bacterial cells, thus resulting in a significant degree of therapeutic synergy capable of eradicating viable bacteria, including those contained within a biofilm, all without adverse side effects.

Poster #8

Aryl Esters of Melampomagnolide B as Anticancer Agents

Shobanbabu Bommagani, Jessica Ponder, Craig T. Jordan, Michael J. Borrelli, Meenakshisundram Balasubramaniam, Robert Reis, and Peter A. Crooks

We have shown that sesquiterpene natural products containing an α-methylene-γ-butyrolactone moiety can be developed as promising anti-cancer agents for the treatment of a wide range of malignancies. Conjugates of Melampomagnolide B (MMB), a naturally occurring sesquiterpene lactone isolated from *Magnolia grandiflora*, exhibit remarkable potency in anticancer screens carried out by the National Cancer Institute. A biotin ester conjugate of MMB has been shown to selectively target proteins associated with the NFκB and glutathione pathways in acute myelogenous leukemia stem cells. Importantly, MMB has extremely low cytotoxicity towards normal hematopoietic stem cells. These intriguing results directed our attention to design and synthesize a library of aryl ester conjugates of MMB and to evaluate them for anticancer activity against a broad range of both hematological and solid human cancer cell lines. From these studies, eleven compounds were identified as potent anticancer agents with growth inhibition (GI_{50}) values in the nanomolar range. The most promising compounds fell into the category of heteroaryl esters of MMB. These compounds were also tested for their cytotoxicity against rat CNS 9L-SF gliosarcoma cells (glioblastoma). The results indicated that two ester analogs were found to be 60,000-fold and 10,000-fold, respectively, more toxic than the clinical drug DMAPT against rat 9L-SF gliosarcoma cells in culture, and were considered potential clinical candidates for the treatment of both hematopoietic and solid tumors.

Poster #7

Combretastatin A-4 and Apysinopsin Analogs as Lead Anti-cancer Agents

Narsimha R. Penthala, Grace Coggins, Maddukuri Leena; Jessica H. Hartman, Dae Song Jang; Alexei G. Basnakian, Suja arattuthodiyil, Kevin M. Raney, Nikhil R. Madadi, Thirupathi R. Yerramreddy, Rajashekar Konjeti, Michael L. Freeman, Robert L. Eoff and Peter. A. Crooks

Cancer is one of the leading causes of morbidity and mortality worldwide, and is the second leading cause of death globally, responsible for 8.8 million deaths in 2012. By 2030, the global burden is expected to grow to 21.7 million new cancer cases and 13 million cancer deaths due to the growth and aging of the world population. The future cancer burden will probably be even larger because of the adoption by developing countries of Western lifestyles, such as smoking, poor diet, physical inactivity, and fewer childbirths.

Dr. Crooks' group has had a strong focus on the design and synthesis of novel small molecule derivatives of natural products over several decades. One such area of focus has been on the development of combretastatin A-4 and aplysinopsin analogs as anti-cancer agents for treatment of both hematological and solid tumors. The combretastatin A-4 analogs have been developed as tubulin targeting agents, whereas the aplysinopsin analogs have been developed as radiosensitizing agents. These studies on small molecule analogs of natural product as anti-cancer agents has resulted in the filing of 10 patents (US 2010/0081678A1; PCT Int. Appl. WO 2014105957 A1, 20140703, 2014; PCT Int. Appl. WO 2014172363 A2 20141023, 2014; PCT Int. Appl. WO 2014176351 A1 20141030, 2014; PCT Int. Appl. WO 2015153635 A1 20151008, 2015; EP13868363A, 2016; EP2986596, 2016; US 20160068506A; US 20160075689A1 and EP2988598A4, 2016; US 20170015635 A1) in the US, Europe and other countries around the world. Dr. Crooks' research group is collaborating with both National and International distinguished cancer research scientists to develop clinical candidates for treatment of a wide range of hematological and solid tumors.

Poster #2

Design and Synthesis of Bcl-xL Degraders as Potent Senolytic Agents

Xuan Zhang, Yingying Wang, Daohong Zhou, and Guangrong Zheng

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Accumulating evidence indicates cellular senescence plays an important role in many age-related pathologies. Thus, selective clearance of senescent cells (SCs) is considered to be a promising strategy for the delay and treatment of age-related diseases. We recently identified Bcl-xL as a target for the development of small molecules, termed as senolytic agents that can selectively kill SCs. Herein, we report the utilization of an emerging technology in drug discovery, known as Proteolysis Targeting Chimera (PROTAC), to design small molecules that can recruit Bcl-xL proteins to E3 ubiquitin ligases for induced degradation. PROTACs could be more efficacious than their corresponding conventional inhibitors owing to their catalytic nature in inducing protein degradation and their ability to deplete protein levels rather than transiently block an active site. Our PROTACs are based on A1155463, a potent and selective Bcl-xL inhibitor.

Most of our designed PROTACs showed excellent Bcl-xL binding affinity. One of the lead compounds, **XZ13906,** selectively killed ionizing radiation induced senescent human WI38 fibroblasts while sparing normal WI38 cells (EC_{50} = 2.4 uM for IR-SCs, > 100 uM for normal cells, SI >42). Western blot analysis confirmed that **XZ13906** degraded Bcl-xL protein in a dose and time dependent manner. To the best of our knowledge, this is the first study to demonstrate efficacy with PROTACs in a cellular aging model.

Poster #3

Assessing the Interest of UAMS Investigators in fastPACE Biomedical Commercialization Course

Nancy Gray, Ph.D., Nancy Rusch, Ph.D., Curtis Lowery, M.D.

UAMS is gauging faculty interest in the fastPACE Course, a 4-week biomedical commercialization course designed for busy researchers and clinicians with early stage projects.

Created by FastForward Medical Innovation at the University of Michigan and modeled after the successful NSF I-Corps program, fastPACE blends in-person and online education to help researchers and clinicians learn the basics of biomedical commercialization and prepare a successful business case for funding and development partnerships. The course is open to anyone with early stage innovations or ideas, including clinicians, researchers, postdocs, graduate students and medical students. Participants will have the opportunity to develop a successful business case to secure funding and attract collaborators and determine the commercial viability of their innovation. The fastPACE Course features an expert interdisciplinary teaching team from academia and industry. Project teams are divided into educational tracks and assigned a teaching team member to capitalize on their unique experience and maximize mentorship opportunities. More than 70 project teams have graduated the fastPACE Course and used their experience to secure additional funding, find collaborators, submit publications, and conduct additional research. We would like to replicate those results at UAMS. Contact Nancy Gray for more information or to express interest: nmgray@uams.edu.

Poster #6

Valchlor gel (Mechlorethamine): an approved FDA drug in the USA, and marketed in Europe as Ledaga for the treatment of Mycosis fungoides and cutaneous T-cell lymphoma (MF-CTCL)

Zaineb AF Albayati, Vipin P Nair, Sundar Neelakantan, David R Worthen, Marhaba Hojahmat and Peter A Crooks

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), a rare form of non-Hodgkins lymphoma. It has no cure, and its cause is unknown. The malignant T-cells migrate to the skin, causing lesions to appear. Lesions first appear as a rash and then may grow into disfiguring tumors. MF is an uncommon disease, with an incidence of less than 1 per 100,000 person-years in the U.S.A. The low incidence of the disease makes clinical studies more challenging. Valchlor, a topical formulation of mechlorethamine is a breakthrough medicine for intervention in stage 1A and 1B of MF-CTCL. Valchlor is formulated in a unique way to chemically stabilize mechlorethamine and keep it from entering a patient's bloodstream. Topical application of Valchlor in patients with MF-CTL has shown that 60% of patients demonstrated 50% improvement and 48% of Valchlor-treated patients achieved complete skin remission of their skin lesions within 1-12 months of treatment. In summary, Valchlor is the first and only FDA-approved topical formulation for the topical treatment of MF-CTCL. Recently, mechlorethamine gel (Ledaga) was also approved by the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) for the treatment of MF-CTCL in adult patients.

Poster #5

Novel Potent Anti-leukemia Stem Cell Compounds

Paola E. Ordóñez, Krishan K. Sharma, Laura M. Bystrom, Ujwani Nukala, Rajeskumar Manian, Maria A. Alas, William F. Reynolds, Raul G. Enriquez, Darcy C. Burns, Omar Malagón, Darin E. Jones, Michael Balick, Shraddha Thakkar, Philip J. Breen, Monica L. Guzman, Paola E. Ordóñez, Krishan K. Sharma, Laura M. Bystrom, Ujwani Nukala, Rajeskumar Manian, Maria A. Alas, William F. Reynolds, Raul G. Enriquez, Darcy C. Burns, Omar Malagón, Darin E. Jones, Michael Balick, Shraddha Thakkar, Philip J. Breen, Monica L. Guzman and Cesar M. Compadre

Standard chemotherapy against acute myelogenous leukemia (AML), has remained largely unchanged, and most patients with AML die of their disease despite initially achieving complete remission. In addition, these approaches have shown cardiac toxicity limiting their use in elderly patients. These treatments fail to eliminate quiescent leukemia stem cells (LSCs) providing a reservoir for disease relapse. Thus, it remains an important priority to identify compounds that may specifically ablate the LSC population with decreased overall toxicity. One potential source of less toxic agents is compounds that occur naturally in plants. It is estimated that approximately 25% of prescription drugs are plant-derived (e.g. taxoids (cancer), artemisinin (malaria). In this context, we have designed a paradigm that relies on a combination of chemotoxanomy and ethnobotany to identify potentials sources of new anti-leukemic compounds. This approach has lead us to the discovery of multiple new compounds and to the discovery of novel compounds with potent demonstrated anti-AML activity, low toxicity, and activity in an animal model.

Poster #4

Development and Commercialization of Tocol-containing Pharmaceuticals

Ujwani Nukala, Shraddha Thakkar, Awantika Singh, Nukhet Aykin-Burns, Rajeshkumar Manian, John House, Guangrong Zheng, Sanchita Ghosh, Mahmoud Kiaei, Marjan Boerma, Martin Hauer-Jensen, Philip J. Breen and Cesar M. Compadre

There is a pressing need to develop safe and effective radioprotector/ radiomitigator agents for use in accidental or terroristic radiological emergencies. Naturally occurring vitamin E family constituents, termed tocols, include members, such as the tocotrienols. The tocotrienols have remarkable radiation-protection properties with minimal toxicity. Unfortunately the tocotrienols have very short plasma half-lives and require dosing at very high levels to achieve necessary therapeutic benefits. The short elimination half-life of the tocotrienols is related to their low affinity for the α-tocopherol transfer protein (ATTP), the protein responsible for maintaining tocol plasma levels. In an effort to uncover tocotrienol analogues with enhanced binding to ATTP, we developed a computational approach for the virtual screening of those analogues. Our approach, based in molecular dynamics simulations, overcomes the limitations of other computational approaches. Based on this approach, we developed of a new class of vitamin E analogues, the tocoflexols, which maintain the superior bioactivity of the tocotrienols and have the potential to achieve longer half-life and larger AUC of the tocopherols.