Showcase of Medical Discoveries:

# *Training Grant Research*


**Wednesday, February 10, 2016**
**4:30—6:00 p.m.**

***A Wine & Cheese Reception Featuring UAMS Investigators Discussing their Research and Discoveries.***

Winthrop P. Rockefeller Cancer Institute, 10th Floor Rotunda

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**Poster #1**

## *Systems Pharmacology and Toxicology T32*

Philip R. Mayeux, PhD, Director

The Systems Pharmacology and Toxicology (SPaT) training program at UAMS is supported by the NIGMS grant T32 GM106999. SPaT is designed for PhD students pursuing dissertation research projects in the pharmacological sciences. The T32 supports 2 new and 2 continuing students each year and the College of Medicine and the Translational Research Institute together support one additional position. Trainees are drawn from three PhD programs: Pharmacology, Interdisciplinary Toxicology and Interdisciplinary Biomedical Sciences. The SPaT program is unique in that it trains students to use an *in vivo* approach to answering relevant questions in pharmacology and toxicology with emphasis on metabolism, drug design, pharmacodynamics, pharmacokinetics, and signaling to complement the cellular and molecular training students receive in their home programs. The rationale for SPaT is that this type of training provides students with a much broader perspective on pharmacology and toxicology that better prepares them to be leaders of multidisciplinary research teams in the pharmacological sciences. Training faculty come from the Colleges of Medicine, Pharmacy and Public Health, the Arkansas Children's Hospital, and the National Center for Toxicological Research. The SPaT program also provides strong mentoring, extensive networking, and teaching and leadership opportunities for its trainees through its programmatic activities.

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**Poster #2**

***Preclinical Evaluation of the Phosphodiesterase-4 Inhibitor, Rolipram, in an Infant Model of Sepsis-Induced Cardiorenal Syndrome***

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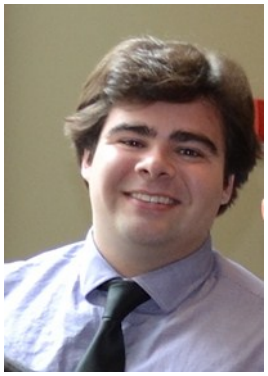
Clark R. Sims – Gradate Student

Multi-organ failure is a frequent complication of infant sepsis. Sepsis-induced cardiorenal syndrome (type 5), defined as development of acute cardiac dysfunction and acute kidney injury, is a frequent complication of infant sepsis that dramatically increases mortality. To define the apparently unique pathogenic mechanisms contributing to renal and cardiac failure during septic shock in infants, and identify targeted therapies to reverse them, we developed a rat pup (17-19 days old) model of infant cardiorenal syndrome induced by cecal ligation and puncture (CLP), a model of infant sepsis that replicates the key cardiorenal abnormalities. Rolipram is a phosphodiesterase-4 inhibitor shown to reduce renal vascular resistance and improve microvascular perfusion in an adult mouse model of sepsis. The therapeutic potential of rolipram was evaluated using intravital video microscopy and echocardiography following CLP in our rat pup model. Rolipram was administered at the time of CLP and cardiorenal syndrome was assessed at 18 hours. Rolipram prevented renal hypoperfusion and also prevented sepsis-induced decline in stroke volume, left ventricular velocity, fractional shortening, ejection fraction, and most importantly, cardiac output. The protection by rolipram on perfusion and cardiac output indicate that rolipram may be therapeutically beneficial in infant cardiorenal syndrome.

**Poster #3**

## *Dietary Antioxidants Counteract Ethanol-Induced Morphological Changes in Bones of Female Mice*

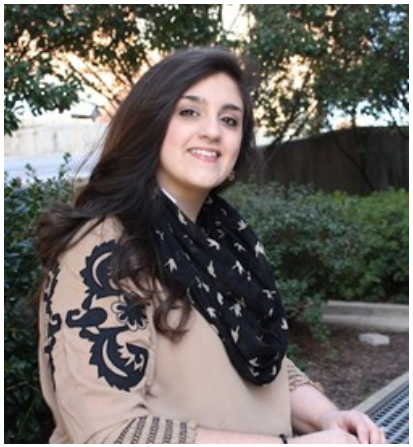


Alex W. Alund – Gradate Student

Chronic alcohol consumption leads to an elevated risk of osteoporosis as well as increased fracture risk by decreasing bone mineral density through increasing bone resorption and decreasing bone formation due, in part, to an increase in reactive oxygen species (ROS) produced by NADPH Oxidases (NOX). We hypothesized that different dietary antioxidants, curcumin, N-acetyl cysteine (NAC), and vitamin E (α-tocopherol) would be able to attenuate the NOX derived ROS effects on bone due to chronic alcohol intake. In this study, female mice received a high fat (35%) Lieber DeCarli liquid diet supplemented with an antioxidant with or without EtOH at 30% of total calories for 8 weeks. MicroCT analysis showed a significant decrease in trabecular bone volume and number, and a significant increase in trabecular spacing with EtOH compared to pair-fed (PF). Tibias were stained for nitrotyrosine, an indicator of intracellular damage by ROS, and tibias from mice fed EtOH had significantly more staining compared to PF. In contrast, the EtOH+NAC and EtOH+α-tocopherol did not statistically differ from their respective PF. *Ex vivo* sections of EtOH also significantly increased the size and number of marrow adipocytes per mm as well as mRNA expression of AP2, an adipocyte marker in bone. NAC was able to reduce the number of marrow adipocytes to PF levels while vitamin E and curcumin were not as effective. EtOH fed mice exhibited reduced bone length and reduced number of proliferating chondrocytes within the growth plate. NAC and Vitamin E prevented this. These data show that alcohol's pathological effects on bone extend far beyond decreasing bone mass.

**Poster #12**

## *Association of an EMT with Aggressive Vulvar Squamous Cell Carcinoma*



**Emily Holthoff** – Graduate Student

Factors that contribute to aggressive behavior in vulvar squamous cell carcinoma (vSCC) are poorly defined; however, studies have shown that vSCC with an infiltrative pattern of invasion are associated with worse outcomes compared to those with nested/pushing patterns of invasion. In many tumors, an epithelial-mesenchymal transition (EMT) is associated with tumor progression. This study proposes that infiltrative vSCC may acquire increased aggressive behavior through EMT-like changes. Immunohistochemistry was used to compare EMT-associated indices, including nuclear β-catenin localization, increased vimentin expression, and loss of E-cadherin, in vSCC cases with an infiltrative, a nested/pushing, or a "mixed" invasive pattern. We found that in the majority of infiltrative tumors, these indices were predominant indicating increased EMT. In contrast, these indices were less prominent in the nested/pushing tumors. The association of an EMT with an infiltrative pattern of invasion in vSCC suggests that development of an EMT drives the more aggressive behavior in this subset of tumors.

**Poster #11**

## *Does Proteasome Activation Damage Mitochondria During Renal Cold Storage Plus Transplantation?*

Nirmala Parajuli and Lee Ann MacMillan-Crow

Renal transplantation is the preferred modality of treatment for end-stage kidney disease. Prolonged cold storage (CS) is considered to be a risk factor for long-term transplant outcome. The precise molecular mechanisms responsible for CS related renal damage are largely unknown. Our laboratory demonstrated that renal CS induced oxidative stress and mitochondrial dysfunction, which were blunted by the mitochondria-targeted antioxidant, Mitoquinone (MitoQ). In the current study, we tested the hypothesis that CS-induced mitochondrial reactive oxygen species (ROS) triggers proteasome activation, which leads to mitochondrial and renal damage following transplantation. New studies show increased proteasome activity after CS plus transplantation, which was blunted by addition of MitoQ during CS. Excitingly, addition of Bortezomib, a clinically relevant proteasome inhibitor, during renal CS increased ATP levels, and decreased cell death after transplantation. These results indicate that mitochondria are a target for oxidant induced proteasomal damage during renal CS plus transplantation.

**Poster #4**

## *Neuropathic Pain in Pregnancy*

Shona L. Ray-Griffith, MD; Pedro Delgado, MD; Everett P. Magann, MD; and Zachary N. Stowe, MD

Neuropathic pain (NP), pain caused by injury to neural pathways resulting in aberrant neuronal firing and pain signaling, affects more women than men (REF); and the effect of NP in pregnancy is unknown. The treatment of NP during pregnancy is a clinical conundrum complicated by limited data, reproductive safety concerns, limited treatment options, and the lack of scientifically derived guidelines. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and effective treatment for NP; and has been used to treat depression during pregnancy.

The proposed study aims to: 1) Characterize the course and pharmacological management of NP in the peripartum period; 2) Compare obstetrical and neonatal outcomes of pregnant women with NP versus non-neuropathic pain and controls and; 3) Determine the acceptability, tolerability, and effectiveness of rTMS for the treatment of NP in pregnancy.

We will enroll pregnant women with pre-existing pain (NP and non-neuropathic pain) in a prospective, longitudinal study and collect analgesic exposure data, determine associations with selected outcomes, and compare outcomes between subject groups based on pain type and treatment exposures.

The novel results will be germane to the clinical care of pregnant women with NP and provide a foundation for evidence-based care guideline development.

**Poster #5**

## *Intracellular Mechanisms Modulating Gamma Band Activity in the Pedunculopontine Nucleus (PPN)*


B. Luster, F.J. Urbano, and E. Garcia-Rill

The pedunculopontine nucleus is a major element of the reticular activating system. Our previous *in vitro* studies showed that all PPN neurons tested fired at gamma frequencies and are due to N- and P/Q-type $Ca^{2+}$ channels. Further studies showed that the PPN has three populations of neurons expressing N-type $Ca^{2+}$ channels only, P/Q-type $Ca^{2+}$ channels only, or N- and P/Q-type $Ca^{2+}$ channels. The present study was designed to determine the intracellular mechanisms subserving cells with N-type $Ca^{2+}$ channels in the PPN.

Membrane oscillatory activity was recorded using *in vitro* patch-clamp techniques and 1-sec depolarizing current ramps.

We found that all PPN neurons tested (n=25) showed beta/gamma oscillations when depolarized. In a population of PPN neurons (n=14), H-89 and ω-Agatoxin-IVA combined to inhibit the presence of gamma oscillations ($df=27$, $F=20.11$, $p<0.05$). In another population (n=4), H89 had no effect on gamma oscillations while ω-Agatoxin-IVA completely blocked them ($df=7$, $F=12.52$, $p>0.05$). In a third population (n=7), H89 blocked gamma oscillations while ω-Agatoxin-IVA had no effect on them. These results suggest some PPN neurons manifesting gamma activity through N-type $Ca^{2+}$ channels are mediated by the cAMP pathway.

**Poster #10**

## *Perceived Social Support and Socioeconomic Status Predict Maternal Delay Discounting Behavior and Neural Function in Healthy Postpartum Women*

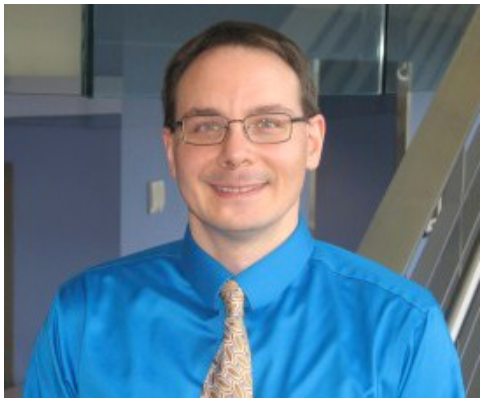
Lisa K Brents, Jonathan Young, Bettina T Knight, Jessica L Coker, Shona L Ray-Griffith, Zachary N Stowe, G Andrew James, Clint D Kilts

Mothers evaluate and execute decisions regarding temporally contingent outcomes daily. Delay discounting (DD), which is the tendency to devalue delayed rewards, is exaggerated in people with drug use disorders. DD has not been studied in early postpartum mothers. This study seeks to understand peri-natal drug abuse by examining the normative behavioral and neural representations of maternal delay discounting for oneself and child. We hypothesized that DD in healthy postpartum mothers is correlated with variables associated with maternal drug abuse, including stress, socio-economic status (SES), perceived social support (PSS), and mother-infant bonding. Multiple regression models that predicted DD behavior were further hypothesized to predict the neural correlates preceding each choice type (immediate or delayed). Healthy women ages 15-45 within 2 months of a full-term delivery (n= 17) were assessed for the variables of interest and completed a novel maternal DD task during a functional magnetic resonance imaging (fMRI) scan.

Impaired bonding and SES significantly ($p < 0.007$) predicted 44% of variance in DD for self. Controlling for PSS reduced the influence of impaired bonding and SES. Ethnicity, PSS and SES predicted 35% of variance in a delayed choice-specific deactivation in the right dorsolateral prefrontal cortex, a region crucial to executive function. Results indicate that maternal PSS and SES play important roles in postpartum maternal decision making.

**Poster #9**

## *Translational Training in Addiction (T32 DA022981)*



G. Andrew James, Ph.D. and Clint Kilts, Ph.D.

The goal of the UAMS NIDA T32 training grant "Translational Training in Addiction" is to provide multi-level, transdisciplinary, team science training that spans the gamut of molecular to community-based components of translational addiction research. Towards this goal, the T32 program objectives are to (1) develop a shared knowledge of the scientific, clinical and societal roles and impact of drug use disorders, (2) provide an individualized path of addiction research career development preparing trainees for careers in diverse workforce settings, (3) provide learning environments emphasizing interdisciplinary, team science and translational research, (4) provide grounding and training in research ethics and diversity, (5) remove barriers to independence and career goal-congruent post-training placement, (6) monitor trainee and program progress, and (7) develop addiction physician scientists. The T32 supports multiple levels of training in addiction including predoctoral trainees (PhD), postdoctoral trainees (PhD), psychiatry residents (MD), and medical student summer internships – thus providing broad, diverse, and truly translational training opportunities in addiction research and treatment.

**Poster #6**

## *Diversity Outbred Mice Indicate Idiosyncratic Drug-induced Liver Injury Potential*

Lascelles Lyn-cook, Jr., Daniel M. Gatti, Shaoke Luo, Gary A. Churchill, and Alison H. Harrill

Hepatotoxicity is a major cause of attrition during pharmaceutical development. While newer models have offered improvements in predicting incidence of common hepatotoxic events, the ability to detect idiosyncratic (low frequency) drug-induced liver injury (DILI) has remained elusive. There is a need for animal models that can detect liver liabilities that are genetically mediated. The Diversity Outbred (DO) mice comprise a genetically diverse population with variability that surpasses that of the human population. We hypothesized that the DO could provide a model for low frequency DILI in patient populations. In this study, female DO mice (N=50/group) were administered orally one of three drugs associated with rare liver toxicity that are still used clinically (diclofenac, zileuton, isoniazid) or 0.5% methylcellulose vehicle. Mice were dosed (i.g.) daily up to 14 days and blood samples were taken before dosing and at necropsy. As a group, diclofenac and zileuton both caused significant elevations in alanine aminotransferase (ALT) from the pre-dose (baseline) values at necropsy ($P<0.05$). ALT was not elevated by 0.5% methylcellulose ($P>0.05$). While preliminary, the data provide an important first step to qualifying the DO mouse population as a tool for improved prediction of rare safety liabilities that may call for personalized prescribing strategies.

**Poster #7**

## *An Exploratory Sequential Study to Develop an Assessment of Factors Influencing Implementation of Best Nutrition Practices among Early Childhood Educators*

Taren Swindle, Zachary Patterson and Carrie Boden-McGill; Mentors: Leanne Whiteside-Mansell and Wendy Ward

This study applied a novel theoretical model to the development of an exploratory sequential research design which (a) included in-depth interviews with educators (qual) to (b) inform the development of a new measurement tool to assess factors likely to predict implementation practices (QUANT). Qualitative interviews with 29 ECEs were completed and coded using directed content analysis with Belsky's model providing sensitizing concepts. The principal investigator and one research assistant completed coding after reaching 85% agreement on a random sample of 5 interviews.

We have identified 16 prominent themes within the 3 theoretical constructs. Using language from the interviews, we have developed an extensive bank of items for instrument development. The next steps of our study will be to (a) solicit stakeholder and content expert input on the item bank, (b) collect surveys from approximately 300 educators, (c) conduct psychometric analyses of the items and proposed scales, and (d) perform structural equation modeling to assess overall model fit. This research will help to improve the early childcare environment for the purpose of promoting nutrition and healthy weight for families affected by poverty.

**Poster #8**

## *Nutritional Approaches to Improve Physical Function in Geriatric Heart Failure Patients*

Bryce Marquis, Ph.D.

Cardiac muscle weakens with age, decreasing its functional capacity and increasing the likelihood of heart failure (HF). HF is a condition where the heart's ability to contract and/or relax is impaired limiting the cardiovascular system's ability to deliver blood and oxygen to where it is needed. In turn, this condition contributes to progressive muscle loss and increased risks for further disease. HF is prevalent in the elderly, comprising 6-10% of the population over the age of 65 and carrying a 35% risk of death within the first year of diagnosis. Exercise is an effective treatment strategy but HF patients suffer from reduced respiratory efficiency which limits their mobility and ability to exercise. This respiratory inefficiency is in large part due to the impaired mitochondrial oxidative capacity found in HF patients. My work aims to improve this oxidative capacity using nutritional therapies that have been previously found to be effective treatment strategies for other diseases where mitochondrial energetics are diminished. These therapies are designed to increase mitochondrial protein turnover and biogenesis while improving oxidative substrate availability. Initial studies will evaluate the effects of essential amino acid supplementation on mitochondrial oxidative capacity and mitochondrial metabolite flux. Exercise capacity will be evaluated in order to determine functional changes. The results of this work will direct the development of a new nutritional approach that can be used alone or synergistically with exercise to improve health outcomes in HF patients.