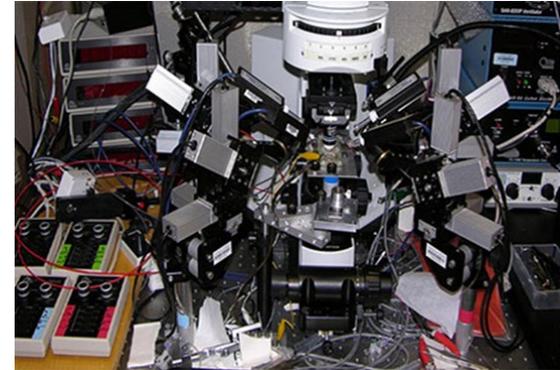*Showcase of Medical Discoveries*

A Focus on Translational Neuroscience Research

**Wednesday
May 15, 2019
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

UAMS

Translational Research from NIGMS: A Decade of Progress

R. Whit Hall, MD, Edgar Garcia-Rill, PhD, Jimmie Birdsong, RN

Background: Arkansas has poor health outcomes including a high infant mortality. Telemedicine can improve access in rural states, leading to improved outcomes, especially in Very Low Birthweight (VLBW, <1500 grams) neonates .

Methods: A Telemedicine Core was established through COBRE funding within the Center for Translational Neuroscience to complete translational research projects and improve newborn health.

Results: Peds PLACE, a pediatric educational conference, occurring once weekly to more than 15 sites was established along with telenursery to improve perinatal regionalization. This initiative decreased deliveries of VLBW neonates in inappropriate nurseries leading to a significant decrease in infant mortality from 8.5 to 6.8 deaths/1000 live births statewide.

Fifty publications and 48 abstracts and presentations have described these findings.

Conclusions: The Telemedicine Core has decreased infant mortality and improved the life of Arkansas' citizens through education, research, and clinical programs designed to reach rural providers.

Poster #11

Class II Histone Deacetylases Require P/Q-type Ca2+ Channels and CaMKII to Maintain Gamma Oscillations in the Pedunculopontine Nucleus

Francisco J. Urbano, Verónica Bisagno, Susan Mahaffey, Sang-hun Lee, and Edgar Garcia-Rill

Epigenetic mechanisms (i.e., histone post-translational modification and DNA methylation) play a role in regulation of gene expression. The pedunculopontine nucleus (PPN), part of the reticular activating system, manifests intrinsic gamma oscillations generated by voltage-dependent, high threshold N- and P/Q-type Ca2+ channels. We studied whether PPN intrinsic gamma oscillations are affected by inhibition of histone deacetylation. We showed that, a) acute in vitro exposure to the histone deacetylation Class I and II inhibitor trichostatin A (TSA, 1mM) eliminated oscillations in the gamma range, but not lower frequencies, b) pre-incubation with TSA (1mM, 90-120 min) also decreased gamma oscillations, c) Ca2+ currents (ICa) were reduced by TSA, especially on cells with P/Q-type channels, d) a HDAC Class I inhibitor MS275 (500 nM), and a Class IIb inhibitor Tubastatin A (150-500 nM), failed to affect gamma oscillations, e) MC1568, a HDAC Class IIa inhibitor (1mM), blocked gamma oscillations, and f) the effects of both TSA and MC1568 were blunted by blockade of CaMKII with KN-93 (1mM). These results suggest a cell type specific effect on gamma oscillations when histone deacetylation is blocked, suggesting that gamma oscillations through P/Q-type channels modulated by CaMKII may be linked to processes related to gene transcription.

Poster #2

Metabolic Control of Reproduction through the RNA-binding Protein Musashi: Translational Regulation of the Pituitary Gonadotrope

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Angela Odle, Ana Rita Silva Moreira, Anessa Haney, Linda Hardy, Melody Allensworth-James, Michael G. Kharas, Christopher J. Lengner, Melanie C. MacNicol, Gwen V. Childs and Angus M. MacNicol

The reproductive axis is sensitive to nutritional cues, such as the adipokine leptin. Individuals with too much (obese) or too little leptin are susceptible to reproductive difficulties. However, the specific mechanisms behind leptin's regulation of reproduction are not known. We have previously shown that deleting leptin receptors (LEPR) in the pituitary cells that secrete luteinizing hormone (LH) and follicle stimulating hormone (FSH) causes a decrease in the vital gonadotropin-releasing hormone receptor (GnRHR) protein (but not mRNA) expression in female mice. This receptor is critical for receiving a signal from the hypothalamus that orchestrates a well-timed pattern of LH and FSH release. We therefore hypothesized that leptin signals to the pituitary regulate reproduction via GnRH translation. In this study, we identify a novel regulator of gonadotrope function, the RNA-binding protein Musashi (MSI). Our results indicate that MSI may repress *Gnrhr* translation, and that leptin is needed to relieve this repression.
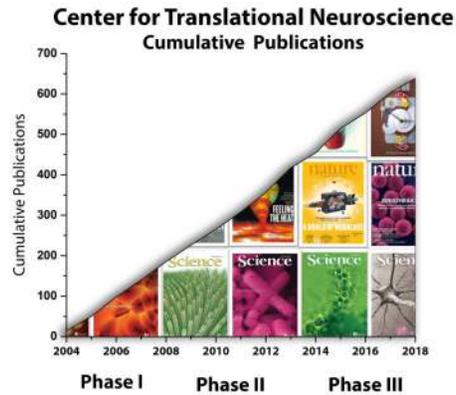
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Poster #3

Center for Translational Neuroscience, 15 years of Progress

E. Garcia-Rill, PhD, CTN Director

The Center for Translational Neuroscience (CTN) is a truly translational COBRE designed to bring cures and treatments rapidly from the lab to the bedside. We support clinician scientists and close to clinical implementation basic research. We established the CTN to provide support for self-sufficient research cores, and to sustain a collaborative, multidisciplinary research environment including pilot study projects, comprehensive mentoring program, and training in translational research.

During Phases I, II and III, we helped UAMS investigators generate $127,004,213 in new funding, published 639 articles and chapters, and secured 2 patents. Our advances included: Charlotte Yates, PT, PhD, developed two new therapies for hyper-reflexia; Mark Mennemeier, PhD, developed an effective intervention for tinnitus; Edgar Garcia-Rill, PhD, discovered a new mechanism for the essential stream of information required for many of our actions; Paige Beck, PhD, found the cellular action for leptin's effect on sleep; and R. Whit Hall, MD, developed a telemedicine system decreasing infant mortality across the state. This program saves ~60 babies/year, >500 babies since we began.

The CTN developed independent research cores with alternative funding and helped scientists achieve research independence. We are grateful for the support from the IDeA program, without which such advances would never have happened.

Poster #10

Safety and Pain Response in Preterm Neonates Receiving Kangaroo Care

Richard W. Hall, Charlotte Yates, Anita Mitchell, and David K. Williams

Kangaroo Care (KC), holding a neonate with skin-to-skin contact, has been shown to be safe and effective in providing pain relief in stable neonates greater than 30 weeks gestational age (GA) when undergoing painful procedures. It is unknown if KC is safe in younger neonates or if it can decrease neonatal pain beyond the immediate time of being held. We sought to determine if KC was safe/effective in decreasing pain scores in preterm neonates younger than 31 weeks GA.

Preterm neonates between 27—30 weeks GA inclusive and > 1000 grams were randomized to receive either 2 hours of KC, defined as skin-to-skin contact in an upright position or Standard Care (SC), defined as no more than 15 minutes of KC daily for 5 days between day of life 5 and 10. There were 19 neonates in each group, for a total of 38 subjects.

KC was safe in neonates weighing more than 1000 grams who delivered after 27 weeks GA. KC did not change PIPP scores after suctioning in preterm neonates if they were not being held at the time of the painful stimulus. PIPP scores after suctioning were high enough to need treatment for pain during suctioning.

Poster #9

Mobile Application, "WeTrain911" to Decrease Stroke Mortality by Enhancing Emergency Dispatcher Training

Aliza T Brown, Jay Im, Richard W. Hall, Edgar Garcia-Rill

Background: In rural states there are shortages of medically trained public safety answering point (PSAP) 911 answering stations. We developed a smart phone medical education application for PSAP operators in underserved rural areas with a high deficiency of medical training. In Arkansas, 93% of 911 dispatchers have no medical training. Following app training, certification of dispatchers in six test deployment sites that improve 911 call speed will be regarded as a success.

Hypothesis: The PSAP personnel serving as dispatch operators who utilize a medical dispatch training app will provide training based medical information, and reduce mortality due to stroke, trauma, and ST-elevation myocardial infarction (STEMI).

Methods: In our data analysis, we are identifying whether the app intervention training influences telecommunication transition of information such as patient condition and caller location information to emergency medical service (EMS) providers. Other variables include paramedic impression/observation coding and response time to the scene. Baseline data from 2012 to 2014 will be used to compare pre- and post-training and state mortality data for stroke, trauma, and STEMI. Dispatcher to EMS agencies for dispatcher/caller information pre- and post-training will be compared for stroke, trauma, and STEMI mortality data.

Results: Currently, 89% of PSAP operators in five test counties have completed certification training.

Conclusion: Data collection is in process.

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Poster #4

D-amphetamine Withdrawal Paradigm in Methamphetamine Dependence

M. Mancino, J. McGaugh, J. Thostenson, K. Williams, and A. Oliveto

Treatment-seeking methamphetamine(METH)-dependent individuals were enrolled in a 4-wk, double-blind, placebo-controlled, residential trial examining the impact of abruptly terminating oral d-amphetamine (DEX) administration in METH dependent humans on at least weekly assessments of withdrawal, sleep, and cognition. Participants were inducted onto DEX during week 1, randomized to receive DEX or placebo (PLA) during weeks 2-3, then PLA during week 4. 14 METH-dependent volunteers completed at least 2 weeks of the study. Except for DEX subjects being older, baseline characteristics did not differ between groups. Preliminary analyses indicate "desire for METH" scores showed a main effect of group at the end of week 2. MAWA score and METH Selective Severity Assessment (MSSA) score showed a trend toward a group main effect at the end of week 2. There were also trends toward time x group interaction for MAWA, MSSA and sleep quality ratings. Significant decreases in supine, seated and standing HR between weeks 1 and 2 occurred in the PLA, but not DEX, group. To our knowledge, this is the first double blind, PLA-controlled trial measuring effects of abruptly stopping amphetamine in METH dependent humans.

Prefrontal and Parietal Recruitment During the MSIT Attention Task Predicts rTMS Outcome in Patients with Subjective Tinnitus

G. Andrew James, Jeff Thostenson, Gwendolyn Carter, Ginger Brown, and Mark S. Mennemeier

Subjective tinnitus is the intrusive phantom perception of sound with no discernible etiology. Patients in an repetitive transcranial magnetic stimulation (rTMS) clinical trial anecdotally reported reduced awareness (but not intensity) of phantom sounds, suggesting subjective tinnitus may be a disorder of selective attention. To test this hypothesis, a prospective subset of patients in the rTMS trial underwent an functional MRI (fMRI) selective attention task prior to rTMS intervention. We evaluated if pre-intervention recruitment of attentional resources predicted post-rTMS treatment response – specifically, a change in tinnitus awareness.

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Decreasing Mortality One App at a Time

Aliza Brown, Whit Hall, and Edgar Garcia-Rill

Population based studies from the National Center for Health Statistics indicate that the overall US stroke and myocardial infarction (MI) mortality rates have been steadily declining in the last two years. However, this decline in mortality is not indicated in minority population subgroups. Instead disparities in both stroke and in MI have continued to persist among African Americans, especially among the younger generations. Both disease subtypes occur more often in younger men than women although mortality rates are higher in women. High mortality rates in both diseases are further compounded by trauma mortality rates especially in rural areas. Geographical disparity is more dramatic for minorities. Our goal, supported by the Center for Translational Neurosciences (CTN) Telemedicine Core, of decreasing the risk of geographical and minority disparities in stroke, MI and trauma for minorities can be achieved by a mobile application that directly transfers patient information and location to area 911 dispatchers. The mobile application iClick, sends patient information and location information to dispatch operators for immediate relay to local EMS providers. Thus, decreasing dispatch-caller interrogation time, missed calls, and decreased transport time by emergency services. We test marketed iClick in the rural Delta areas of Arkansas and are presently collecting information on 911 response calls. We hypothesize the mobile application will increase prompt hospital delivery, increase treatment rates and ultimately decrease stroke, MI and trauma related mortality rates.

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Developmental RNA Regulatory Protein, Musashi, Required for Pituitary Somatotrope Metabolic and Reproductive Functions

Melody Allensworth-James, Angela Odle, Michael G. Kharas, Christopher J. Lengner, Melanie C. MacNicol, Gwen V. Childs and Angus M. MacNicol

Pituitary cells possess remarkable plasticity to change their cell fate and alter hormone production in response to changing environmental cues, however the underlying molecular control of this plasticity has not been established. The Musashi (MSI) family of RNA regulatory proteins governs stem cell fate, but we have also shown that MSI is present in differentiated hormone producing cells of the adult pituitary. MSI was shown to bind MSI binding elements (MBEs) in the 3' UTRs of prolactin (*Prl*) and Pit1 (*Pou1f1*) and suppress translation. To determine the role of MSI *in vivo*, MSI1 and MSI2 were selectively ablated in pituitary somatotropes. Loss of MSI function in somatotropes causes increased fat depots, subfertility, and promoted overexpression of pituitary growth hormone and prolactin in mutant males. However, serum levels of these hormones were low, suggesting that the cells had a secretion defect. We propose that MSI may control not only pituitary stem cell function, but also regulate hormone production and terminal differentiation of cell populations within the adult pituitary.

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Differential Gait Progression in Idiopathic Parkinson's Disease with and without Freezing of Gait

Aliyah Glover BS, Lakshmi Pillai MS, Shannon Doerhoff APRN, and Tuhin Virmani MD, PhD

Objective: To develop a predictive algorithm for freezing of gait (FOG) in Parkinson's disease (PD) through longitudinal objective gait assessments.

FOG results in a significant worsening of quality life for PD patients. FOG is exhibited by the feet "sticking to the ground" for several seconds during active movement. Studies suggest that about 50% of patients develop FOG by 5 years of onset. The ability to predict FOG would allow us to test therapies to prevent development or slow progression.

PD subjects with (FOG) and without (no-FOG) freezing of gait and healthy controls (HC) walked at their normal pace on a 20'x4' Zeno pressure sensor impregnated mat every 3-6 months in the medication ON-state. Data was collected and analyzed using PKMAS software. FOG subjects had a faster decline in mean stride length, mean foot strike length, mean stride velocity, mean swing phase percent compared to no-FOG. The rate of change in mean integrated pressure applied during a footstep, mean stride width, and mean single support phase percent was similar between the PD groups.

FOG subjects demonstrate a differential decline in gait, with faster decline in stride length, stride velocity, foot strike and swing phase percent compared to no-FOG subjects. Early detection of this differential regulation may help predict the development of FOG.

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