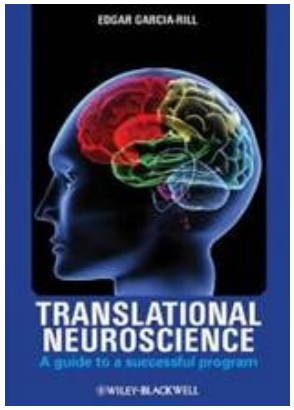
Poster #13

CENTER FOR TRANSLATIONAL NEUROSCIENCE

Bringing Cures from the Bench to the Bedside



AUTHORS: Paige Beck, PhD, Edgar Garcia-Rill, PhD, R. Whit Hall, MD, Mark Mennemeier, PhD, and Charlotte Yates, PT, PhD, UCA

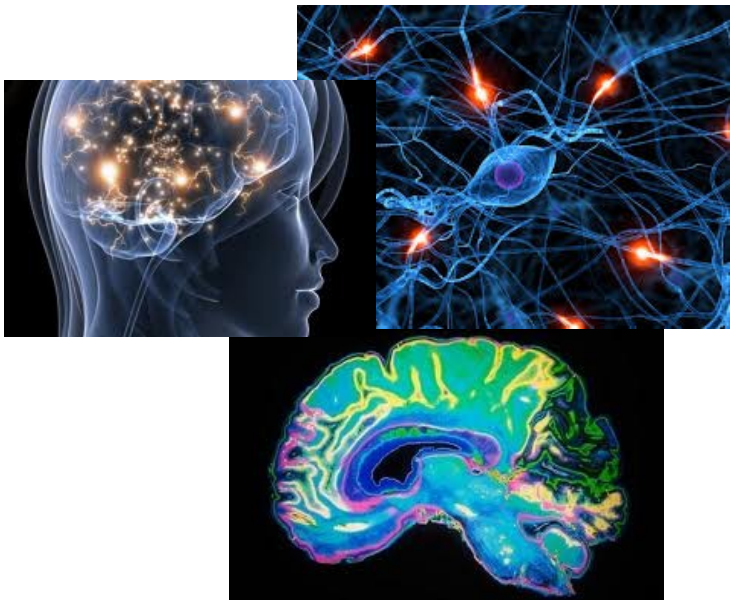
E. Garcia-Rill, PhD, Dept. of Neurobiology & Developmental Sciences
Center for Translational Neuroscience, UAMS

The Center for Translational Neuroscience is a Center of Biomedical Research Excellence (COBRE) funded by the IDeA Program of the National Institute for General Medical Sciences. It is designed to bring cures and treatments rapidly from the lab to the bedside. During our first 10 years, we helped UAMS investigators generate $32, 842, 635 in new funding, published 418 articles and chapters, and secured 2 patents. A few of our advances involve: **Spinal Cord Injury: Calming excessive reflexes-** Charlotte Yates, PT, PhD, developed two new therapies for hyper-reflexia; **Tinnitus: A new treatment for a common ailment-** Mark Mennemeier, PhD, developed an effective intervention for "ringing in the ears"; **Sleep-waking: Novel mechanism for preconscious awareness-** Edgar Garcia-Rill, PhD, discovered a new mechanism for the essential stream of information required for many of our actions; **Obesity: The mechanism of leptin and sleep dysregulation-** Paige Beck, PhD, found the cellular action for leptin's effect on sleep; and **Telemedicine: Peds PLACE saves 60 more babies per year-** R. Whit Hall, MD, developed a statewide system that decreased infant mortality across the state. A number of other advances can be seen on our website. http://www.uams.edu/ctn/

UAMS College of Medicine Series

Showcase of Medical Discoveries:

A Focus on Neuroscience



Wednesday, March 19, 2014
4:00—5:30 p.m.

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

Winthrop P. Rockefeller Cancer Institute
10th Floor Rotunda

UAMS
COLLEGE OF MEDICINE
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

Poster #1

Nuclear Receptor Agonists: Potential Novel Therapies for Multiple Sclerosis

Paul D. Drew, PhD, Jihong Xu, Janet A. Chavis, Gail Wagoner, James C. Douglas, Cindy X. Zhang-Gandhi, Michael K. Racke, and Thomas P. Burris

Multiple sclerosis (MS) is an inflammatory autoimmune disorder characterized by demyelination in the central nervous system (CNS). MS is the leading cause of neurological deficits and disabilities in young adults, and more than 2.5 million people are currently diagnosed with MS worldwide. Treatments for MS are limited and there are no cures for the disease.

We have demonstrated that nuclear receptor agonists show potential as novel therapies for MS. We demonstrate that agonists of nuclear receptors including peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs) and retinoid receptors suppress neuroinflammation by a variety of mechanisms.

For example, nuclear receptor agonists suppress glial cell activation and the production of cytokines and other pro-inflammatory molecules that are believed to contribute to MS. Nuclear receptor agonists also alter the phenotype of autoreactive T cells that are believed to initiate disease.

Finally, nuclear receptor agonists suppress the development of experimental autoimmune encephalomyelitis, and animal model of MS. Collectively, these studies suggest that nuclear receptor agonists may be effective in the treatment of MS.

Poster #12

Paradoxical Effects of Serine Racemase Knockout in the G93A mSOD1 Mouse Model of Amyotrophic Lateral Sclerosis (ALS).

Misty M. Thompson, Ron L. Reed, Patrick Bennett, John C. Marecki, Stephane Marinesco, Stephen W. Barger and John P. Crow

Amyotrophic lateral sclerosis (ALS) is a fatal adult-onset disease characterized by selective death of motor neurons in the spinal cord leading to paralysis of voluntary muscles. In the presence of mutant Cu,Zn-superoxide dismutase (SOD1), motor neurons are subjected to glutamate excitoxicity via the NMDA receptor. The naturally-occurring amino acid L-serine is converted to D-serine by the enzyme serine racemase (SR), which is primarily located in microglia and astrocytes surrounding the synapse. D-serine binds to the NMDA receptor and greatly enhances the affinity for glutamate, thereby potentially causing excitotoxicity without any change in glutamate levels *per se*. Because SR is the primary source of D-serine *in vivo*, changes in protein/activity should slow the rate of neurodegeneration in ALS.

To test this hypothesis, we crossed the $SOD1^{G93A}$ mice with an $SR^{-/-}$ mouse to determine if D-serine deficiency would delay symptom onset and/or extend the survival interval in the ALS model. Surprisingly, the ALS mice with 50% reduction in SR ($SR^{+/-}$:$SOD1^{G93A}$) displayed symptom onset 13 days earlier than $SOD1^{G93A}$ controls, and the $SR^{-/-}$:$SOD1^{G93A}$ mice displayed symptoms 26 days earlier than controls. However, the mean survival interval for the $SR^{+/-}$:$SOD1^{G93A}$ and $SR^{-/-}$: $SOD1^{G93A}$ mice was 60.5±2.2 days and 81.2±4.9 days, respectively. This study suggests that the death of motor neurons may result from changes in D-serine content leading to an exacerbation of motor neuron glutamate excitotoxicity.

Poster #11

The Cognitive Connectome Project: Mapping the Neural Representation of Normative Variance in Cognition

G. Andrew James, Tonisha E. Kearney-Ramos, Jennifer L. Gess, Jennifer S. Fausett, Clinton D. Kilts

Functional magnetic resonance imaging's (fMRI) clinical translation requires understanding the neural representation of normative cognitive variance in well characterized samples of healthy adults. We address this need by initiating the Cognitive Connectome Project, which pairs clinically validated neuropsychological assessments of cognition with canonical functional neuroimaging tasks. We have acquired a demographically diverse sample of 52 participants [29 females; mean (sd) age = 32 (10) years, age range= 19-50 years]. Participants completed a battery of neuroimaging tasks and neuropsychological tests spanning the following cognitive domains: motor ability, visuospatial perception, attention, language, memory, affective processing, decision making, and executive function. We present brain-behavior relationships from the Judgment of Line Orientation (JLO) task, a neuropsychological test of visuospatial perception that we directly replicated as an fMRI task. JLO accuracy was significantly correlated inside and outside the MRI scanner ($r=0.75$, $p<0.0001$), indicating valid replication. Overall, JLO significantly recruited the dorsal visual network ($t>6.4$). However, dorsal visual activity negatively regressed to JLO accuracy ($t<-2.7$, $p<0.01$), suggesting that participants who performed best recruited this network less. Median-split analysis showed poorly performing participants to have more variable brain activity. We conclude by presenting a methodological framework for studying normative brain-behavior relationships and extending these findings into clinical decision-making.

Poster #2

Novel Animal Models of Epilepsy for the Development of the Next-generation Antiepileptic Drugs

.

Fang Zheng, Ph.D., Kevin D. Phelan, Ph.D., and

Epilepsy afflicts over 2 million Americans. Despite more than 6 decades of modern research, current antiepileptic drugs are largely anticonvulsive, and a third of epilepsy patients are refractory to current therapeutic options. There is a pressing clinical need to discovery antiepileptogenic drugs.

There is an emerging consensus that antiepileptogenic drugs need to be screened in a true animal model of epilepsy, (i.e. a model in which seizures are spontaneous and recurrent). We are developing a novel mouse model of epilepsy based on our preliminary data that spontaneous recurrent seizures were induced after administration of a single low dose of pilocarpine in the absence of pilocarpine-induced Status Epilepticus (SE) and detectable neurodegeneration.

A 2nd model of epilepsy is based on our preliminary data that a single amino residue substitution that abolishes the high affinity zinc binding site in the NR2A subunit of N-methyl-D-aspartate (NMDA) receptors causes spontaneous recurrent seizures in mice.

These novel models of epilepsy make it easy to screen novel AEDs directly on their ability to prevent recurrent seizures. They could fundamentally change how epileptogenesis is viewed and how future antiepileptic therapy should be targeted, developed and tested.

Poster #3

Fetal Alcohol Spectrum Disorders (FASD): Discovery of Neuroinflammation and Therapeutic Intervention

Cynthia J.M. Kane, PhD, Kevin D. Phelan,PhD, Jennifer Johnson, James C. Douglas, Lihong Han, Gail Wagoner, Renea R. Smith, and Paul D. Drew , PhD

Maternal alcohol consumption during pregnancy can cause Fetal Alcohol Spectrum Disorders (FASD). FASD occurs in 1/100 births in the U.S. and is the leading cause of mental disabilities. There is no treatment for FASD. Our goal is to prevent or treat the consequences of FASD. Using a mouse model that is equivalent to the third trimester of human gestation, we have discovered that not only neurons but also microglia, an important cell type in the brain, are targets of alcohol in the developing brain. Specifically, alcohol causes major loss of neurons and microglia, microglial activation, and neuroinflammation. We have undertaken studies to discover pharmaceutical drugs that will prevent or treat FASD. Based on our studies, drugs that block neuroinflammation offer meaningful hope. For example, our studies indicate that an FDA-approved pharmaceutical, the anti-inflammatory PPAR-g agonist pioglitazone, blocks alcohol-induced loss of neurons and microglia, microglial activation, and neuroinflammation. It is now important to define the long-term consequences of neuroinflammation for FASD, to establish the therapeutic window for treatment with anti-inflammatory drugs, and test whether other anti-inflammatory drugs can block alcohol-induced neuroinflammation. These studies may lead to novel therapies to prevent or treat FASD.

Poster #10

Neuroprotection in Acute Ischemic Stroke: the Beneficial Effects of Dodecafluoropentane Emulsion

J. Stephen Nix, Sean D. Woods, Christine M. Arthur, Robert D. Skinner, Howard P. Hendrickson, Aliza T. Brown, John D. Lowery, Michael J. Borrelli, William C. Culp

Stroke is a major cause of disability in the US, and is the 4th leading cause of death. A neuroprotectant extending the window for safe thrombolytic therapy would have a profound impact. Dodecafluoropentane (DDFPe) is a liquid emulsion of nanodroplets with potential for a safe, simple, and effective means of reducing infarct volume by transporting oxygen to vulnerable ischemic tissue.

Two animal models of stroke were used to measure the pharmacokinetics and efficacy of DDFPe in stroke neuroprotection. Rabbits (N=55) underwent angiographic embolization of the middle cerebral artery (MCA) and were randomized to receive various doses of DDFPe (0, 0.1, 0.3, 0.6 ml/kg, every 90 min) and sacrifice times (7 or 24 hrs post-stroke). Tissue distribution was measured in 11 rabbits by headspace sampling/GC-MS. Rats (N=42) were used in a similar experiment, using cauterization of the MCA, followed by DDFPe treatment and neurological assessment and sacrifice at 6 hrs.

DDFP promptly reaches the brain and concentrations rise linearly with repeated doses. Infarct volumes were significantly decreased for all DDFPe groups compared with controls in both animal models ($P \leq 0.009$). DDFPe significantly improved neurological testing in the rats ($P \leq 0.01$).

DDFPe provides significant neuroprotection during acute stroke by delivering oxygen to vulnerable ischemic tissue and decreasing infarction. Rapid clinical development may revolutionize early stroke therapy.

Poster #9

Human Myelin Proteolipid Protein Intron 1 Contains an Enhancer Essential for PLP1 Expression

Hamdan H, Kockara NT, Haun S, Wight PA

The myelin proteolipid protein (PLP) is the most abundant protein in CNS myelin. Besides its structural role in myelin, PLP serves important neuroprotective functions. Additionally, the protein has been proposed to be an immunogen for multiple sclerosis (MS). Unlike other myelin genes, there is a gene dosage effect with *PLP1*; adverse conditions occur from either too much or too little (null) expression in humans. However, not much is known about the mechanisms that control human *PLP1* (*hPLP1*) gene expression. To address this matter, mice were generated which harbor the 6.2hPLP(+)Z/FL transgene. The transgene uses *hPLP1* genomic sequences (proximal 6.2 kb of 5′-flanking DNA to the first 38 bp of exon 2) to drive expression of the *lacZ* reporter gene. Results presented here indicate that a 1.5-kb segment of intron 1 is crucial for *PLP1* expression. This segment contains a purported enhancer called wmN1. The wmN1 region in man also overlaps two supplementary exons (AB and C) that get incorporated (separately) through alternative splicing. The mouse *Plp1* gene (*mPlp1*) does not contain counterparts to these supplementary exons due to the lack of conserved splice sites. RT-PCR results indicate that these supplementary exons are utilized in 6.2hPLP(+)Z/FL mice. The splice variants are developmentally regulated in brain, with higher levels at P2 than P21. These novel isoforms may be important for axon-oligodendrocyte communication and/or oligodendrocyte development, and could unwittingly become a target of immune-mediated neurodegeneration in MS.

Poster #4

Ethanol Exposure and Cerebellar Development

Dwight R. Pierce, PhD, College of Pharmacy, Kim Edward Light, PhD, College of Pharmacy, Abdallah Hayar, PhD, College of Medicine, Xiong Lin, graduate student, College of Medicine

Substantial numbers of children are born each year having experienced damage to their brain subsequent to maternal ethanol exposure. Along with neuronal death, alterations in the morphological and functional development of various neurons in the brain may be experienced leading to various levels of impairment of the child. We utilize a rat model system that involves timed ethanol exposure during the third trimester period of cerebellar vulnerability to characterize the nature and extent of damage to the ongoing development of those neurons that escape immediate death. Our focus includes important morphological, molecular, electrophysiological, and functional impacts of this developmental ethanol exposure with the idea of generating approaches for therapeutic restoration or mitigation of the damage. The overarching goal of our research is to use the principles and therapeutic restorations identified as effective from our studies and apply these to addressing the needs of those children suffering similar types of brain damage. The purpose is to improve the lives of those children who have been exposed to ethanol during their development.

Poster #5

Selective Control of Stem Cell Function in the Brain

MacNicol, M.C., Cragle, F., Montales, T.M., Cragle, C.E., Hardy, L.L., Penthala, N.R., Janganati, V., Borreli, M., Simmen, R.C.M., Crooks, P.A. and MacNicol, A.M.

Neural stems cells are rare brain cells that serve the purpose of repairing brain tissue damage. Neural stem cells can both perpetuate themselves (self-renew) throughout life and they can form the different types of cells required for brain tissue growth and repair. Neural stem cells have tremendous potential for therapeutic treatment of brain injury caused by insults such as Alzheimer's disease, Parkinson disease and stroke.

Paradoxically, neural stem cells are also more likely to cause brain cancer than ordinary brain cells because they last the life of the organism and can slowly accumulate DNA mutations that make them prone to initiate tumors. Recent work has demonstrated that brain tumors contain rare subpopulations of cells that possess stem cell function (so-called “cancer stem cells”). Unfortunately, these cancer stem cells are resistant to current chemotherapy and radiation regimes and contribute to tumor recurrence after treatment.

In our work, we seek to identify novel drugs that will promote the survival of healthy neural stem cells but will prevent growth of cancer stem cells. Our long-term goals are to reverse cancer stem cell function to eliminate brain tumor growth and to aid neural stem cell function for therapeutic repair of brain injury.

Poster #8

A Novel Therapeutic Target to Enhance Synaptic Plasticity in Alzheimer’s Disease

Paul E. Gottschall, PhD, Matthew D. Howell, Michael A. Cozart, Brenda M. Gannon, Dept. of Pharmacology and Toxicology, College of Medicine

Lecticans are chondroitin sulfate (CS)-bearing proteoglycans deposited in extracellular regions adjacent to synaptic active zones. The presence of lecticans near synapses may constrain functional and structural changes in post-synaptic dendritic spines that occur during the formation and consolidation of memories. In Alzheimer’s disease (AD) brain, pathological senile plaques consist of aggregated forms of the peptide Aβ, and certain isoforms of Aβ are toxic to synapses. We have shown that Aβ binds avidly to lecticans, Aβ inhibits lectican degradation, and lecticans are overexpressed in the brain of AD subjects. In an AD mouse model, removal of CS from lecticans reversed the synaptic decline observed around plaques and diminished Aβ deposition. Blocking lectican cell signaling using the drug, fasudil, reversed the decline in spatial memory observed in AD mice. Overall, this suggests that the presence of excess lecticans at the synapse is detrimental to synaptic function in AD. The broader goal is to assess whether removal of lecticans, or reduction in lectican signaling is a critical therapeutic mechanism that may be used for drug development in AD. Since all currently approved drugs for AD merely treat symptoms, treatment that may retain functional synapses would be a significant step forward to inhibit disease progression.

Poster #7

I Think I was Irradiated but I Cannot Recall?

Antiño R. Allen, PhD, Dept. of Pharmaceutical Sciences, College of Pharmacy

A unique feature of the space radiation environment is the presence of high-energy charged particles such as 56Fe. These may pose a significant hazard to space flight crews not only during the mission but also later, when slow-developing adverse effects could finally become apparent. The hazards associated with the space environment will impact many organs/ systems, and in the central nervous system (CNS), radiation exposure is known to significantly affect the hippocampal formation, a structure critical for cognitive function.

The underlying mechanisms for radiation-induced cognitive impairments are unknown, but may involve altered neurogenesis, inflammation, loss of mature neurons in the dentate gyrus, alterations in NMDA subunits and genetic risk factors. Our lab and others have reported that heavy ion irradiation has a significant effect on neurogenic cells. Data are starting to accrue suggesting that specific microenvironmental factors like inflammation and oxidative stress are associated with this effect, both after photon irradiation and particulate irradiation. Establishing how low dose 56Fe irradiation affects neurogenesis and other factors associated with cognitive function is crucial for our understanding of performance decrements in individuals exposed to irradiation in the space environment.

Poster #6

"Does Diabetes Predispose One to Alzheimer's Disease… or Vice Versa?"

Steven W. Barger, Ph.D., Rachel D. Hendrix,
Bounleut Phanavanh, and Jordan Walters

Type-2 diabetes mellitus (T2DM) is a growing health-related concern, in part because of increases in its incidence. However, T2DM is also significant because of emerging evidence regarding the breadth of its effects on various body systems. It is now recognized that T2DM is associated with CNS deficits such as dementia, including Alzheimer's disease. Most investigators have hypothesized that the problems associated with high blood glucose and other irregularities of metabolism lead to the development of Alzheimer's. However, our most recent evidence suggests that the converse may be true. Specifically, we have found several ways in which a gene related to Alzheimer's creates diabetic tendencies. The amyloid precursor protein (APP) serves as the source of amyloid β-peptide (Aβ), the material that accumulates in Alzheimer brain plaques; mutations in APP cause some cases of Alzheimer's disease. We found that a secreted derivative of APP (sAPPα) binds and activates insulin receptors, and mice devoid of the APP gene were protected against development of the prediabetic syndrome that mice would otherwise exhibit when fed a high-fat diet. But other fragments of APP may contribute to T2DM too, as mice producing human Aβ in their central nervous system neurons develop a prediabetic state (insulin resistance) by default. Moreover, when placed on a high-fat diet, these Aβ-producing mice show severe abnormalities in their blood levels of both insulin and glucose. We are currently surveying the tissues of these mice for biochemical markers of insulin resistance, and we are assaying their blood for hormones that regulate appetite and energy utilization. We are also testing a line of mice that overproduces sAPPα in its brain to determine whether this derivative of APP counteracts the effects of Aβ. This project will ultimately test drug candidates that impact these interactions and thus provide novel therapeutic opportunities for Alzheimer's and T2DM.