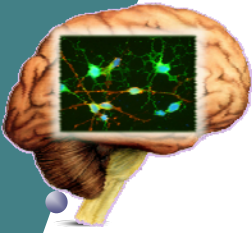


# USUHS Neuroscience Newsletter



Volume 16, Issue 1

September 2008

[WWW.USUHS.MIL/NES/HOME.HTML](http://WWW.USUHS.MIL/NES/HOME.HTML)

## Neuroscience Welcomes Four New Students In 2008!

**Craig Budnich:** Craig attended undergraduate school at The University of South Alabama and graduated with a BSN in 1994. He attended the US Army Graduate Program in Anesthesia Nursing and received an MSN in 2000. He has been deployed to Afghanistan twice and Iraq once. His special anesthesia interests are field anesthesia, regional anesthesia, and teaching neophyte anesthesia practitioners. His interests in the neurosciences include traumatic brain injury (pharmacologic treatment modalities aimed at ameliorating the effects of traumatic brain injury) and post-traumatic stress disorder. Craig is married and has one two-year-old daughter. He and his wife are expecting another child in February. His hobbies include running, fishing, and taking care of his two-year-old.



From left to right: Craig Bunidich, Trevor Logan, Erik Prager and Camila Almeida

**Trevor Logan:** Trevor came to USU from Harford County Maryland where he lived on the Edgewood area of Aberdeen Proving Ground. He graduated from St. Mary's College of Maryland in May of 2008 where he obtained a B.A. in Biology with a minor in Neuroscience. He spent two years working as an  
*Continued on page 2*

**Eric Prager:** Eric is originally from Denver, CO. He graduated from Penn State in 2005 with a bachelors in psychology and received his Master's in Counseling Psychology. His interests are in post traumatic stress disorder, specifically the micro-anatomy of fear memory and the effects of glucocorticoid receptors on amygdalar synapses.

**Camila Almeida:** Camila is from Rio de Janeiro, Brazil where she obtained her BS in Biomedical Science from the Federal University of Rio de Janeiro. During her undergraduate years she started to study the effect of excitotoxicity on the cholinergic system, focusing on the role of nitric oxide and peroxy-nitrite. After getting her  
*Continued on page 2*

## Student Biographies (Continued from page 1)

Trevor: *(continued from page 1)* undergraduate lab assistant in the college Psychology/Neuroscience lab, where he worked on several rodent behavioral studies. These included studies examining the cognitive abilities of the NVHL model of schizophrenia and of the beta amyloid infusion model of Alzheimer's disease, as well as studies observing the effects of various lesions on a rodent's ability to

acquire a learning set. He hopes to broaden his neuroscience research experience to include studies of neural regeneration and studies in developmental neurobiology. Trevor was a member of his college swim team, enjoys being outdoors, and loves seeing live music.

Camila: *(continued from page 1)* undergraduate degree, she started her Master's at the same University and continued

working on characterizing the neuroprotective effect of polyunsaturated fatty acids against oxidative stress. At the end of her Master's she applied to the Neuroscience Program at USUHS to work in the field of epilepsy research in Dr. Braga's Lab. In July 2007, she got married to Davi and then they came to USA to continue their studies.

## Changes in the Neuroscience Program



Dr. Sharon Juliano (left) and Dr. Regina Armstrong (right)

The neuroscience program welcomes Dr. Sharon Juliano as the Acting Director of the Graduate Program in Neuroscience. Dr. Juliano is a Professor in the Department of Anatomy, Physiology and Genetics. In her role as acting direc-

tor, Dr. Juliano will oversee 44 participating faculty and over 20 Ph.D. students. The program is interdisciplinary and involves faculty and students from a wide range of basic science and clinical departments.

Dr. Juliano takes over the role from Dr. Regina Armstrong, who is now the acting director for the Center for Neuroscience and Regenerative Medicine. *(See page 4)*

## Congratulations Graduates!

### The Influence of Intrinsic and Extrinsic Factors on Neurogenesis By Cheol Lee

Neurogenesis is a complex process through which new neurons are generated. The process is regulated by combination and coordination of cell intrinsic and extrinsic factors. I analyzed the expression and molecular function of an intrinsic factor, the nuclear regulatory protein A + U-rich element-binding factor 1 (AUF1) in the developing brain, and the role of an extrinsic factor, the vascular endothelial growth fac-

tor (VEGF) and its receptor Flk1 in mediating de novo neurogenesis in the injured adult brain. The AUF1 is a known regulator of messenger RNA stability and also acts as a transcription factor upon binding to AT-rich DNA elements. Here I show that AUF1 is specifically expressed in subsets of proliferating neural precursors and differentiating postmitotic neurons of the developing cerebral cortex. Importantly, AUF1 was co-expressed with histone deacetylase 1 (HDAC1)

and metastasis-associated protein 2 (MTA2), members of the nucleosome remodeling and histone deacetylase complex. AUF1 specifically and simultaneously bound to HDAC1, MTA2, and an AT-rich DNA element. These interactions have functional significance because AUF1's gene regulatory function was modulated by the extent of histone acetylation and, in cells lacking AUF1, the composition of the complex was modified. AUF1 was also expressed in de novo neurons in the adult dentate gyrus (DG).

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Dr. Cheol Lee

### The Causes and Consequences of Altered Glucose Metabolism in Cancer

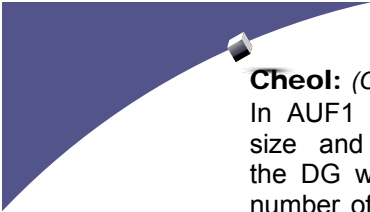
By Thomas McFate  
Altered glucose metabolism as reflected by lactate accumulation despite adequate oxygen availability is commonly associated with malignant transformation. However, the causes and consequences of this link remain unclear. Here we explore possible causes of this metabolic pattern and how they may promote malignancy. The transcription factor Hypoxia Inducible Factor-1 (HIF-1) controls the expression of many genes commonly associated with malignancy, including those which

increase lactate, and its activation in cancer is highly correlated with poor clinical outcome. HIF-1 activation by hypoxia is well characterized; however, its regulation under normoxia in cancer cells is still uncertain. Here we show that elevated glucose metabolites promote normoxic HIF-1 activation via inhibition of its degradation pathway. Since HIF-1 activation results in elevation of the glucose metabolites that inhibit its degradation, we suggest a novel feed-forward mechanism of malignant progression. HIF-1 activation has also been shown to alter glucose metabolism through inhibition of the Pyruvate Dehydrogenase Complex (PDC). The PDC is inhibited by phosphorylation of its regulatory PDH $\alpha$  subunit, and HIF-1 increases phosphorylation through expression of Pyruvate Dehydrogenase Kinase-1 (PDK-1). Here we show that increased PDH $\alpha$  phosphorylation and PDK-

1 expression are associated with malignancy and normoxic HIF-1 accumulation in cancer cells. Furthermore, we show that inhibition of PDK expression by short hairpin RNA (shRNA) results in reversion from the malignant phenotype and normoxic HIF-1 accumulation in cancer cells both in vitro and in vivo. The link between HIF-1, glucose metabolism, PDC activity and the malignant phenotype suggests a novel regulatory pathway and further signifies the importance of abnormal glucose metabolism in malignancy. Dr. McFate is currently working with Dr. Sharon Juliano. His thesis advisor was Dr. Ajay Verma.



Dr. Thomas McFate



Cheol: (Continued from page 3)

In AUF1 mutant animals, the size and cytoarchitecture of the DG were altered and the number of proliferating cells in the DG was reduced, suggesting that AUF1 is a regulator of neurogenesis both in the developing and adult brain. VEGF is a well-known angiogenic factor and also has neurotrophic effect. In primary embryonic neuronal cultures, Flk1 was expressed in proliferating cells and young neurons, and VEGF had both proliferative and antiapoptotic effects. VEGF receptor Flk1 was expressed by both neuroblasts and by maturing granule neurons in the normal adult DG. The expression of VEGF, but not that of Flk1, was significantly and specifically upregulated in the ipsilateral DG in the injured rat brain. To directly test the role of VEGF and Flk1 in regulating de novo hippocampal neurogenesis, recombinant VEGF or SU5416, an

inhibitor to Flk1, was delivered into the ipsilateral cerebral ventricle of injured animals. VEGF infusion significantly increased the number of de novo granule neurons in the DG but not proliferating cells, suggesting that VEGF in the injured adult brain acts predominantly as a differentiation / survival factor. Interestingly, chronic treatment with SU5416 failed to lower the number of de novo neurons below control levels in the injured brain, suggesting that the observed effect of VEGF may involve mechanisms other than Flk1 activation.

Overall, we found that AUF1 is involved in regulating cortical neurogenesis in the developing brain through interactions with chromatin-remodeling molecules. This suggests a novel role for this already multifunctional molecule. In addition, I have

shown experimental evidence that AUF is also involved in adult hippocampal neurogenesis. I found that VEGF is a mediator of de novo neurogenesis in the injured adult brain and its effect is likely similar to the developing brain. These findings suggest that the regulatory process on neurogenesis by intrinsic and extrinsic factors is conserved between the developing and adult brain. These results will help to identify the genetic and environmental risk factors leading to developmental brain disorders and to develop treatment options to alleviate the consequences of brain injury. Dr. Lee is continuing to work in the laboratory of Dr. Denes Agoston, his thesis advisor.

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## Center for Neuroscience and Regenerative Medicine (CNRM): Uniformed Services University (USU) is developing a new Center for Neuroscience and Regenerative Medicine (CNRM).

Through the CNRM, USU will extend partnerships with the Walter Reed National Military Medical Center, the Defense Center of Excellence for Traumatic Brain Injury and Psychological Health, the Army Medical Research and Materiel Command and the National Institutes of Health to further develop the capacity to address knowledge gaps to improve diagnosis, treatment and rehabilitation across the spectrum of traumatic brain

injury (TBI) resulting from both Operation Iraqi Freedom and Operation Enduring Freedom. The CNRM plan is to develop better diagnostic tools for to characterize the brain injury of each patient through advancing neuroimaging and biomarker technologies for use with other traditional and novel assessment tools. In addition, the CNRM will develop potential therapeutics for TBI through a better under-

standing of neuroplasticity and rehabilitative approaches to optimize recovery of function. Across the spectrum of TBI, neuroprotective strategies will attempt to prevent secondary damage and impairment along with investigation of neuroregenerative approaches that are emerging from recent advances in stem and progenitor cell biology as a potential means to restore lost neurologic function.