



NEUROSCIENCE NEWSLETTER

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Neuroscience Open House— Another success!



Five New Faculty Join Neuroscience Program



Dr. Ying-Hong Feng received his M.D. from Wuhan University, Wuhan, China in 1983 and his Ph.D. in Biochemistry from the University of Oxford, Oxford, England in 1993. He completed his postdoctoral training at the Cleveland Clinic Foundation and Case Western Reserve University in 1999. Dr. Feng was an Assistant Professor at Case Western Reserve University until he joined USUHS in 2003 as an Associate Professor in Pharmacology. Dr. Feng's main research interests are focused on molecular mechanisms of G protein-coupled angiotensin receptors in ligand recognition, activation, signal transduction, desensitization, internalization, nuclear translocation, dimerization, posttranslational modification, and pathophysiological relevance. These projects deal with many diseases or disorders from the view of dynamic protein-protein interaction networks since renin-angiotensin-aldosterone system mediates diverse physiological functions in many organs and tissues. NIH and AHA sponsor these projects. In addition to the main research interests, Dr. Feng's laboratory also works on orphan G protein-coupled receptors, P2X7 receptors, gene targeting, and neurotrophin signaling. Many state-of-the-art technologies in molecular biology, cell biology, biochemistry, pharmacology and bioinformatics are employed as routine in Dr. Feng's research project, i.e., proteomics and functional proteomics and various protein-protein interaction technologies.



Dr. Jack Tsao received his undergraduate degree in biochemistry from Harvard College, a master's degree in biochemistry from the University of Cambridge, a doctorate in physiology/pharmacology from the University of Oxford, and a medical degree from Harvard Medical School. He completed neurology residency at the University of California-San Francisco and was then stationed at Naval Hospital Jacksonville, where he was department head of neurology. While at the Naval Hospital Jacksonville, Dr. Tsao also completed a behavioral neurology fellowship at the University of Florida. He is currently Assistant Professor of Neurology and Neuroscience at USUHS and is actively involved in clinical and basic science research as well as military telemedicine development. Dr. Tsao's research interests include basic mechanisms of synapse and axon degeneration in both developmental and pathological states, the use of Botulinum toxins in the treatment of low back pain and headache, cognitive changes and phantom limb pain in amputees, and the role of anticholinergic medications in the pathogenesis of dementias.



Dr. Michael Schell did his undergraduate work in biochemistry at Indiana University and then worked as a lab technician for 5 years, studying superoxide production in neutrophils and membrane trafficking in liver. He received his Ph.D in Neuroscience in 1997 from Johns Hopkins University, where he trained with Dr. Solomon Snyder and characterized the endogenous D-amino acids in the brain. Dr. Schell then moved to Cambridge, England for 8 years where he completed postdoctoral training with Dr. Robin Irvine. Following postdoctoral work involving inositol phosphates and calcium signaling, he remained in the Dept. of Pharmacology at Cambridge as the Royal Society Case Fellow for Brain Research. Dr. Schell arrived at USUHS in February 2005 as an Assistant Professor in Pharmacology. His lab investigates the cell biology of hippocampal neurons, with a particular emphasis on live-cell imaging and analysis. The current focus is how calcium regulates the actin cytoskeleton of dendritic spines. Dr. Schell also holds a degree in science journalism and has participated in the sport of Ultimate Frisbee for 20 years, at both local and international levels.



Dr. Maria Braga received her Ph.D. in Physiology and Pharmacology from the University of Strathclyde in Scotland in 1993. She then obtained postdoctoral training in the Dept. of Pharmacology and Experimental Therapeutics at the University of Maryland School of Medicine. Dr. Braga came to USUHS as a Research Assistant Professor in the Dept. of Psychiatry and is currently an Assistant Professor in the Dept. of Anatomy, Physiology and Genetics. Dr. Braga's research interests focus on the cellular and molecular mechanisms regulating neuronal excitability in the amygdala, and how alterations in these mechanisms relate to the pathophysiology of anxiety disorders and epilepsy. She recently identified two important mechanisms regulating GABAergic synaptic transmission in the amygdala. These mechanisms involve a direct regulation of GABA release by

presynaptic GluR5 kainate receptors and α_{1A} adrenoceptors. She has also obtained evidence for the clinical significance of these findings. The long-term goal of Dr. Braga's research program is to provide the basic knowledge that is crucial for the development of effective therapeutic strategies aimed at preventing or treating neurological and psychiatric disorders involving the amygdala.

Dr. William Campbell recently joined USUHS as the Chair of the Dept. of Neurology.

Congratulations

Tara Romanczyk was the recipient of the **Award for Best Student/Resident Paper** at the 25th Annual Meeting of the American Society for Laser Medicine and Surgery. She presented her work on "Light as a Replacement for Mitogenic Factors on Progenitor Cells". The meeting was held in Orlando, Florida, March 30 - April 3, 2005.

Tara also received a **United States Air Force travel grant** to attend and present her work at the 2005 Annual Meeting of the American Society for Laser Medicine and Surgery.



Tyler Best was one of two **Platform Presentation Winners** at the USUHS Graduate Student Colloquium. His poster title was "Abnormal Synaptic Function in GIRK2-/- Mice".

Joseph O'Sullivan was one of three selectees for the **President's Poster Session** at the USUHS Graduate Student Colloquium. His poster title was "Effect of Diazoxide (Dz) in an Animal Model of Combined Hemorrhagic Shock and Cerebral Stroke.

Clifton Dalgard was the recipient of the 2005 USUHS **Board of Regents Award for the Graduate Program in Basic Medical Sciences**. The Board of Regents Award is the highest honor a graduating doctoral student can receive.

Ahmed Mohyeldin was honored as the **selected representative to speak** on behalf of all the graduating students in the Graduate Program in Basic Medical Sciences.

Dr. Ajay Verma was awarded the **Outstanding Biomedical Educator Award**

Tida Kumbalasiri was **commissioned into the US Navy** on Monday, 23 May 2005.

USUHS Neuroscience Student Graduates



Ahmed Mohyeldin defended his thesis and completed his PhD in Neuroscience on October 15, 2004, under the mentorship of Dr. Ajay Verma. Much of Ahmed's scientific research focused on hypoxic and metabolic signaling in brain tumors. The rich scientific environment in which he trained in has encouraged him to stay on in the Verma lab as he applies to medical school for his next journey. During his postdoctoral training Ahmed will be part of the Clinical Head and Neck and Functional Neuroscience Course teaching medical and graduate students while continuing to build on many of the seminal discoveries made in the Verma lab.

THE ROLE OF ERYTHROPOIETIN SIGNALING IN HUMAN CANCER

Ahmed Mohyeldin

Directed by Ajay Verma, M.D., PhD

Associate Professor, Department of Neurology

Hypoxia in solid tumors emanates from a structural and functionally disturbed vascular supply. Intratumoral oxygen levels are associated with poor prognosis, treatment resistance and cancer metastases, yet mechanisms for such phenomenon remain poorly understood. The major objective of this dissertation was to test whether or not erythropoietin (Epo), a hypoxia inducible cytokine, plays a role in astrocytoma treatment resistance and progression. The specific aims of this dissertation were to: 1) Determine whether or not hypoxia regulates the expression of Epo and EpoR (erythropoietin receptor) in astrocytomas. 2) Examine if Epo treatment results in treatment resistance in astrocytomas against chemotherapy. 3) Evaluate if Epo signaling promotes invasiveness in human astrocytomas. We examined the expression of erythropoietin and its receptor using immunohistochemistry in human glioma and head and neck tumor biopsies. We also established several *in vitro* cell death and cell invasion assays to examine the effects of Epo signaling on human malignant astrocytoma and head and neck cancer cell lines. In addition, we developed primers to measure baseline and hypoxia-inducible Epo and EpoR mRNA expression in cancer cells with quantitative RT-PCR.

Collectively, this work answers key questions that provide insight into how hypoxia promotes cancer malignancy. Human cancers express Epo as well as functional EpoR. Expression of these proteins is most pronounced in hypoxic tumor regions and in invasive tumor margins. This work demonstrates that recombinant human Epoetin- α can directly stimulate the invasiveness of human cancer cells through Matrigel®. Epo also promotes tyrosine phosphorylation in human glioma cell lines. Hypoxia upregulates the expression of both Epo and EpoR in cancer cell lines and also promotes invasiveness. Moreover, hypoxia-induced invasiveness is blunted in stably transfected cells expressing a truncated form of the Epo receptor and diminished by Epo neutralizing antibodies. Together these findings suggest that autocrine or paracrine Epo signaling may play a significant role in cancer cell invasiveness. Furthermore, the use of Epo to treat anemia in cancer patients may have the deleterious side effect of promoting local cancer spread. Our work may also have profound implications for the treatment and management of cancer patients since Epo is used to treat anemia associated with cancer therapy.

USUHS Neuroscience Student Graduates

Clifton Dalgard completed his Ph.D. in Neuroscience on March 14, 2005. He is currently pursuing exciting postdoctoral opportunities while working on his new home in San Francisco.



HYPOXIA-INDUCIBLE FACTOR HYDROXYLASES ARE OXYGEN SENSORS IN THE BRAIN

Clifton Dalgard

Directed by Ajay Verma, M.D., PhD

Associate Professor, Department of Neurology

In mammalian cells, molecular oxygen is a requirement for normal growth, metabolism, and survival. Tissues in which oxygen demand surpasses oxygen supply become hypoxic and cannot maintain normal function. Thus, the ability to sense oxygen levels is necessary for an organism to survive and thrive in changing environmental and physiological conditions. HIF-1 is a transcription factor complex that is essential and central to several cellular and systemic adaptations to hypoxia. For example, vascular endothelial growth factor and erythropoietin are HIF-1 target genes that are important in angiogenesis and erythropoiesis, respectively. HIF-1 consists of two subunits, alpha and beta, and control of HIF-1 function is accomplished through the hydroxylation of proline residues and an asparagine residue on the α -subunit of HIF-1. Under normoxic conditions, hydroxylated HIF-1 α is constantly and rapidly degraded, thus HIF-1 is inactivated. Additionally, undegraded HIF-1 α is hydroxylated at an asparagine residue in the c-terminal region, which prevents it from binding to the co-transcriptional activator p300. The post-translational modifications of HIF-1 α are performed by four oxygen-dependent enzymes, the three HIF-1 α prolyl hydroxylases (HPH-1, HPH-2, and HPH-3) and the asparaginyl hydroxylase FIH-1 (Factor Inhibiting HIF). Since these enzymes modify HIF-1 α in an oxygen-dependent manner, they have been suggested to function as oxygen sensors *in vivo*. No studies of these oxygen sensors have been conducted in the mammalian brain or brain derived cells. The dissertation describes biochemistry, cellular and molecular biology, and whole animal physiology of these oxygen sensors.

Using human glioma cell lines, we demonstrated that HPHs are themselves induced by hypoxia, thus suggesting the presence of a negative feedback system to modulate hypoxic gene expression. For the three HPHs, we found differential distribution of expression between different brain cell types and different brain regions. The same HPH homologues that are regulated in permanent cell lines are regulated in brain cells in culture and *in vivo*. We found that different brain regions induce HPH expression to different extents and hypoxic induction of the oxygen sensors was more prominent in young animals than in old and was manifested by increases in protein expression and enzymatic activity. We also found in addition to oxygen availability, the HIF hydroxylases are also regulated by certain glycolytic metabolites. We specifically identified pyruvate and oxaloacetate as the regulatory metabolites and demonstrated that their mode of action involves a reversible inactivation of HIF hydroxylation. Pyruvate and oxaloacetate induced HIF-1 in cells and also resulted in upregulation of HPH-1 and HPH-2. These results suggest HIF prolyl hydroxylases are sensor of oxygen tensions as well as glycolytic metabolite accumulation. Moreover, both of these stimuli increase expression of these hydroxylases which may serve as a negative feedback system for these sensing mechanisms. Given that the brain is highly sensitive to low oxygen tensions, these studies may provide valuable insight to develop novel tools and therapies for oxygen-associated brain diseases like stroke, heart failure, and brain cancer.

Local Brain Awareness Week Event

USUHS Neuroscience Faculty & Students Participate

Current and former members of the USUHS Neuroscience Program teamed up with Walter Reed Neurology Residents, NIH faculty, and Society for Neuroscience Headquarters staff, including SfN President, Carol Barnes, to hold a local Brain Awareness week event on March 14, 2005. The event was held at the Francis Junior High School in Washington, D.C. for seventy-five 7th grade science students. The activities were:

(a) Nerve Net: A guided tour of the cybercerebrum through websites teaming with fun discoveries about the brain was directed by representatives from NIMH Neuroinformatics Branch and Labs-Now, LLC.

(b) Neuro-Relay: Current USUHS Neuroscience students, Tom McFate, Sean Manion, and Alisa Schaefer and former students, Drs. Ahmed Mohyeldin and Tammy Crowder, used a relay race to illustrate axonal and synaptic conduction. Teams formed an axon and neuromuscular junction. A basketball was passed from one science student to another along the axonal "nodes of Ranvier". When the action potential reached the synaptic terminal, tennis balls (neurotransmitter) were tossed across the synapse into a series of target holes (receptors). Stray balls were retrieved by a child acting as an astrocyte. When a critical number of neurotransmitters found their receptors, a science student acting as a muscle fiber shot a basketball from the foul line (muscle contraction). The team with the most baskets won.

(c) Piece of Mind: Drs. Verma and Schell, along with current USUHS Neuroscience student Adetoun Adeniji-Adele organized this activity to teach students neuroanatomy and specialization of different brain regions. Posters, model brains, computer animations, and MRI scans as well as real plastinated brains were used in lessons including the anatomy of consciousness, balance, sensation and movement.

Students received the SfN publication, "Brain Facts", and material from the Charles Dana Foundation.

Contributed by Dr. Ajay Verma

A **Special Thanks** is extended to **Dr. Leslie McKinney** for her time and effort in serving on the Executive Committee as well as Course Director for "Introduction to Neuroscience" and "Advanced Techniques & Topics in Neuroscience". We wish her well in her new position at the FDA.

Your Graduate Student Representative

is currently **Tyler Best**. Each USUHS graduate program has a Student Program Representative whose role is to serve as liaison between administration/faculty and graduate students through the dissemination of pertinent information. This position also allows students to raise concerns and issues that can then be addressed through more formal channels. If you have any questions, comments or concerns, please contact Tyler .

Monthly Lunch Group for Graduate Students & Student-run Neuroscience Journal Club

The goals of the monthly lunch group for USUHS Neuroscience graduate students (NSL) are to discuss issues important to graduate students and to facilitate peer support. The Neuroscience Journal Club (JC) aims to keep students abreast of current literature, offers an opportunity to discuss Neuroscience topics and provides an informal setting to practice presenting research. Combination NSL/JC Meetings will be held the 2nd Tuesday of each month during the academic year and JC will be held 2-3 times monthly during the summer. These are informal, student run meetings designed to help graduate students get through their graduate careers. If you have suggestions for a meeting or journal club topic, please contact Alisa Schaefer (aschaefer@usuhs.mil) or Tara Romanczyk (tromanczyk@usuhs.mil).

2005/2006 SCHEDULE (Topics and dates subject to change)

June:	<i>JC:</i>	6/14/05 and 6/28/05
July:	<i>JC:</i>	7/05/05 and 7/19/05
August:	<i>JC:</i>	8/02/05, 8/16/05 and 8/30/05
September:	<i>JC:</i>	9/13/05
	<i>JC/NSL:</i>	9/27/05 Orientation to Grad School: Choosing a Lab, Mentor & Rotations
October:	<i>JC/NSL:</i>	Attending Conferences and Presenting a Poster
November:	<i>JC/NSL:</i>	Finances
December:		Holiday Luncheon
January:	<i>JC/NSL:</i>	Applying for Grants & Fellowships
February:	<i>JC/NSL:</i>	Thesis Writing
March:	<i>JC/NSL:</i>	Oral Presentations

The Neuroscience Newsletter welcomes **Tom McFate** as our new **Student Editor**. Tom will serve to assist in gathering information for the Newsletter as well as act as the point of contact for students wishing to submit accomplishments and / or other information. We welcome Tom to our team.

2004/2005 Neuroscience Program Executive Committee

Regina Armstrong, Ph.D.	Program Director, Anatomy, Physiology & Genetics	301-295-3205
Martha Faraday, Ph.D.	Medical Psychology	301-295-9671
Sharon Juliano, Ph.D.	Anatomy, Physiology & Genetics	301-295-3673
Leslie McKinney, Ph.D.	Anesthesiology	301-295-3021
Aviva Symes, Ph.D.	Pharmacology	301-295-3234

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Suzanne Bausch, Ph.D.	Editor, Pharmacology	301-295-3226
Tina Finley	Editorial assistant, Neuroscience	301-295-3642