The last three months since the last newsletter have been an exciting time in our department.

Our Teaching is in full swing and has already met with success in the exams. The student feedback tells us that our enthusiastic and committed Faculty and support staff continue to excel.

Our contributions to the Graduate Program are also notable and we are looking forward to celebrating the December graduation of Jessica Crawford, Avinash Thirumalai, Yan Wang and Joe Wu. PhD studies at times may seem like a long road and I wish them perseverance over the next few months and wisdom in finding the right “next step” in their career. We are honored and proud to have been part of their ongoing development as scientists.

Our Mentoring Program of research students was also very successful at the undergraduate and medical student level, as was evident from their presentations at the Summer Life Science Symposium and the Summer Medical Student Research Day. I am grateful to Dr. Ecay and Dr. Hoover, for their leadership in the undergraduate and medical student summer research programs, respectively. Our research program continues to improve.

Our Internal Seminar Series is a wonderful venue to present our work, share ideas, foster new collaborations and receive feedback on our plans. Our two external speakers were inspiring and we will continue to host similar leading scientists in this seminar series. We were particularly pleased to welcome back Dr. Cory Leonard, a former student of Dr. Hayman in our department, who gave an impressive special seminar.

Our new Biomedical Sciences Journal Club has grown into something very special, with outstanding papers from different areas of research being presented by trainees and interested Faculty members. (Continued on page 2)
Chair’s Comments (Cont’d.)

Last but not least, we celebrate together with Drs. Zou and Hoover for being awarded R15 NIH grants. Our research is going to benefit tremendously from the new state-of-the-art Leica SP8 confocal microscope in the Microscopy core, which was recently installed. Our gratitude goes out to Dr. Hoover, Rolf Fritz, TJ Neal and Robin Montgomery for making this possible. We invite any and all at ETSU to use our Core facilities, knowing that this will promote our University’s research mission.

Of course, our Teaching, Research, and Service is nothing without our people. To accomplish what we currently do and what we strive for, we rely on people. Therefore, it is exciting to be part of a recruitment drive for five Faculty positions in which we are hoping to attract new colleagues who can join us in our mission.

On a personal note, I would like to again take the opportunity to extend our sympathies to several of our team who mourned the loss of loved ones. May you be strengthened by being among your co-workers. There also was much joy and laughter in our department. This is also true in our family, especially since our two adopted children from Ethiopia came home after a lengthy process. We thank all who supported us with encouraging words and prayers, and continue to do so. So, yes, team Biomedical Sciences continues to do very well and I am very happy to be part of it.

DR. HAGG AND WIFE, FRANCINE, WELCOME NEW FAMILY MEMBERS

After several months of excited and anxious anticipation, and several trips to Ethiopia, the Hagg family is finally united with their two adopted children. The Hagg family were very happy they were allowed to keep sister and brother together.

Hasset, whose name means “Joy” in Ethiopia, is 7 years old. One of the criteria for the Hagg family was to be able to adopt a child with a disability. Hasset is deaf and all communications is through sign language, which the Hagg family has learned to do quite well in preparation of Hasset’s coming. Yeabsira, whose name means “God Father’s Work” in Ethiopia, is 11 years old.

Dr. Hagg tells us that the children are adjusting quite well, as are the proud parents. As Dr. Hagg pointed out, “The house is filled with laughter and two brains soaking up tons of information.”

Many well wishes are extended to Dr. Hagg and Francine and their new family members.
RECENT JOURNAL PUBLICATIONS


SCIENTIFIC MEETINGS/ INVITED SEMINAR PRESENTATIONS

**Dr. Alok Agrawal**, Professor, served on the “Arthritis, Connective Tissue, and Skin.” Study Section Review Committee, NIH, Baltimore, MD, October 6-7, 2014.

**Dr. Tom Ecay**, Professor, chaired a workshop session titled "The Challenge of Teaching Physiology in a Changing Environment: Innovation and Resources." American Physiological Society Intersociety Meeting: Comparative Approaches to Grand Challenges in Physiology, which was held in San Diego, CA, October 5-8, 2014.

**Dr. Gregory Ordway**, Professor, served as an external reviewer for Academic Program Review of the Pharmacology and Toxicology Graduate Program at East Carolina University, September 21-23, 2014.

**Dr Krishna Singh**, Professor, served on Cardiac Biology Regulation (BSci 5; “Basic and Clinical-Translational Science).” Grant Peer-review committee, American Heart Association, Teleconferencing, October 6, 2014.

**Dr. Richard M. Kostrzewa**, Professor, served as External Examiner for the Ph.D. Dissertation defense of Amber L. Marriott at the Atlantic Veterinary College, University of Prince Edward Island in Charlottetown, Prince Edward Island, Canada, April 15, 2014.

**Dr. Richard M. Kostrzewa**, Professor, presented a seminar at the Atlantic Veterinary College, University of Prince Edward Island in Charlottetown, Prince Edward Island, Canada: “L-DOPA Effects on Striatal Microdialysate Levels of Hydroxyl Radical in Parkinsonian Rats,” April 15, 2014.

**Ms. Jessica Slade**, Graduate Student in Dr. Schoborg’s Lab, will be doing an oral presentation at the 1st ASM Conference on Polymicrobial Infections. The conference is in Washington, DC, November 13-16, 2014. Jessica also received a student travel award to attend this conference. (See abstract)

**DR. KOSTRZEWA RECOGNIZED FOR ACHIEVEMENTS AND BOOK RELEASE**

Dr. Richard Kostrzewa, Professor, has been recognized in the September 2014 issue of “The Pharmacologist” a quarterly publication of the American Society for Pharmacology and Experimental Therapeutics (ASPET), under Achievements, Awards, Promotions, and Scientific Breakthroughs. The article highlights Dr. Kostrzewa’s release and announcement of the 2-volume edition of the *Handbook of Neurotoxicity* (Springer New York), of which he is Editor-in-Chief.

**SOCIETY for NEUROSCIENCE**

*Advancing the Understanding of the Brain and Nervous System*

*Annual Meeting*
*November 15-19, 2014*
*Washington, DC*
**Grant Awards—Congratulations!**

**Dr. Don Hoover, Professor**

**Funding Agency:** NIH  
**Grant Number:** R15 GM107949-01A1  
**Principal Investigator:** Donald B. Hoover, PI; Tammy Ozment, CI.  
**Project Title:** Cholinergic Anti-inflammatory Mechanisms in Sepsis and Septic Shock  
**Award Issue Date:** 8/19/14  
**Project Funding Period:** 9/1/14—8/31/17  
**Total Award:** $337,340

**Project Narrative:** Inflammation plays a central role in many diseases, and its impact is especially evident in patients with a life-threatening infection of the blood (i.e., sepsis). This research uses a preclinical model of sepsis to evaluate cellular and therapeutic responses to a novel drug that works by amplifying the body’s own anti-inflammatory pathway. Such drugs could have broad application to other inflammatory diseases.

**Dr. Yue Zou, Professor, and Ben Hilton, Graduate Research Assistant and Laboratory Director**

**Funding Agency:** NIH  
**Grant Number:** R15 GM112168-01  
**Principal Investigator:** Yue Zou, PI;  
**Project Title:** “Antiapoptotic Role of Ataxia Telangiectasia and Rad3-Related”,  
**Award Issue Date:** 8/18/14  
**Project Funding Period:** 9/1/14—8/31/17  
**Total Award:** $315,840

**Project Narrative:** Ataxia telangiectasia and Rad3-related (ATR) is a member of the PI3K-like protein kinase family and plays a key role in regulating cellular DNA damage responses which are highly relevant to cancer biology. Based on our recent novel finding on ATR’s role in regulation of apoptosis, the goal of this project is to define the molecular mechanisms of the regulation.
2014 ANNUAL FACULTY CONVOCATION

Seven faculty were honored by President Brian Noland at the 2014 Annual Faculty Convocation held on August 22, 2014.

Drs. Scott Champney, Donald Ferguson, and Jeff Ardell were awarded *Emeritus Faculty* status by Dr. Noland:

- **Dr. W. Scott Champney**
  Retired December 31, 2013

- **Dr. Jeffrey Ardell**
  Retired September 30, 2014

- **Dr. Donald Ferguson**
  Retired May 31, 2014

- **Dr. Michelle Duffourc**
  received the College of Medicine Faculty Service Award at the Faculty Convocation

- **Dr. Theo Hagg**
  received an official warm welcome as a new Faculty member and Departmental Chair by Dr. Noland

- **Dr. Cuihong Jia**
  received an official warm welcome as a new Faculty member by Dr. Noland

- **Dr. Tom Kwasigroch**
  was one a handful of Faculty who were highlighted in a tribute to major players throughout the history of ETSU
NEW TECHNOLOGY ENHANCES RESEARCH EFFORTS IN BIOMEDICAL SCIENCES

(Pictures and article compliments of Rolf Fritz, Coordinator, and Dr. Don Hoover)

The ETSU Department of Biomedical Sciences Microscopy Core Facility is located in building 119 on the VA Campus and is comprised of a newly purchased Leica TCS SP8 scanning confocal microscope complete with a stand-alone Alienware computer system for data analysis and processing, and a Philips Tecnai 10 transmission electron microscope.

The new inverted confocal microscope, offered on a “fee-for-service” basis, is a laser powered single-point scanning system capable of producing publication quality high resolution images of fluorescently labeled tissues and cells. The SP8 offers, in addition to standard confocal imaging, a Resonant Scanning capability allowing scans of live cell cultures and deep tissue targets. Differential Interference Contrast (DIC) and brightfield light microscopy is also possible using the Leica system. Confocal microscopy allows the user to obtain data and images from very thin tissue sections as well as sections up to 100 microns in thickness. At least four different colors of fluorescence can be visualized concurrently using a single scan or a compilation of multiple scans through the sequential scanning capabilities of the system. 3D rendering of scanned images is also made possible using a series of Z-stacks obtained from the system software. The core also provides a new Alienware stand-alone computer for the exclusive purpose of allowing confocal users to view and process their confocal data and images while freeing the confocal microscope for use by other investigators, and maintaining the safety and integrity of the main confocal computer.

The electron microscopy facility, located in bldg. 119, room 119, has been in service since 2001 and provides for users a Philips Tecnai 10 transmission electron microscope. The facility offers users the opportunity to observe, on a sub-cellular microscopic level, structures in both normal and experimental tissues and cultured cells. The facility is capable of processing tissue samples and cultured cells, obtaining thin sections of the processed tissue or cells using ultra-cut microtomes, and the subsequent staining and observation of the samples placed onto copper or gold support grids. The facility is also available for processing of clinical biopsy samples as well. Fees are assessed according to the type and the amount of processing done by the core staff.

Use of the core is managed by Dr. Donald Hoover and staff members of the Department of Biomedical Sciences. Training and assistance with use of both the confocal microscope and the TEM are available as needed. Judy Whittimore, Director, phone number (423)-439-6785, located in room 119, and Rolf Fritz, Lab Coordinator, phone number (423)-439-6208, located in room 253 or room 119, will be available for assisting and training users of either microscope.

An Open House will be planned in the near future in order to thank the Administration (Dr. Dean Means, Dr. Ken Olive as Interim Dean, Dr. Wilsie Bishop, Vice President for Health Affairs, and Dr. Brian Noland, President, for helping to make this purchase possible.)
Fibroblasts and the Extracellular Matrix in Cardiac Remodeling

In mammalian tissues, the extracellular matrix does not only serve a structural role, but also transduces key signals to the cells. The extracellular matrix is populated with fibroblasts, mesenchymal cells that produce matrix proteins and are capable of synthesizing cytokines and growth factors. Tissue injury activates fibroblasts and causes profound alterations in the extracellular matrix. Most forms of tissue injury are associated with de novo synthesis of "matricellular proteins", a family of structurally unrelated molecules that do not serve a structural role but bind to the matrix and the cells, regulating cell behavior and modulating signaling cascades. This presentation will discuss the dynamic alterations, interactions and role of the fibroblasts and the extracellular matrix in the remodeling heart. Following myocardial injury, fibroblasts undergo dramatic phenotypic changes and become the dominant cell type in the heart, synthesizing matrix proteins, but also secreting cytokines and growth factors. Deposition of matricellular proteins in the cardiac interstitium drives the cellular responses associated with repair and remodeling of the injured heart. Fibroblast-dependent actions and matrix-mediated effects play a crucial role in the pathogenesis of heart failure following cardiac injury.

Post-infarct remodeling of cardiac sympathetic nerves and arrhythmia

Millions of people suffer a myocardial infarction (MI) every year, and those who survive have increased risk of arrhythmias and sudden cardiac death. Clinical studies indicate that heterogeneity of sympathetic transmission in the heart is arrhythmogenic. We are investigating changes in the cardiac innervation after MI, including neurochemical alterations, nerve sprouting, and axon degeneration in order to identify the underlying mechanisms and determine which changes are pathological vs. protective for the heart.
Cory Leonard, Ph.D.
Postdoctoral Fellow
Department of Pathobiology
Institute of Veterinary Pathology
University of Zurich

Date: October 23, 2014
Time: 11:00 a.m.
Building 178, Small Auditorium
Quillen College of Medicine/VA Campus

Danger Associated Molecular Patterns (DAMPs) inhibit Chlamydia inclusion development

Abstract: The chlamydiae, Gram-negative, obligate intracellular bacteria, cause a broad spectrum of diseases, affecting a wide range of animals, including humans. All chlamydiae share a biphasic developmental cycle, the primary developmental forms of which are infectious elementary bodies (EB) and replicative reticulate bodies (RB). After EB attachment and entry into the host cell, chlamydiae develop within a membrane bound vacuole called an inclusion. Inside the inclusion, EB differentiate into non-infectious RB, undergo multiple rounds of division before re-differentiating into infectious EB, and are released from the host cell via lysis or extrusion. Danger Associated Molecular Patterns (DAMPs) are molecules that stimulate the non-infectious inflammatory response. These molecules of host origin can occur as the result of cellular stress, damage or death in the presence, or absence, of infection. When released into the extracellular milieu, these normally intracellular molecules initiate and potentiate migration and maturation of a variety of immune effectors cells and are typically associated with increased secretion of pro-inflammatory cytokines. Additionally, DAMPs can affect non-immune cells, such as epithelial cells, the target cells for many pathogenic microorganisms such as the chlamydiae. We evaluated the effect of the purine metabolites extracellular ATP and adenosine on Chlamydia (C.) trachomatis and C. pecorum inclusion development by exposing Chlamydia-infected HeLa cells to these DAMPs in vitro. The DAMPs reduced inclusion size, number of bacteria per inclusion and production of infectious EB in both Chlamydia species. The effect was reversible, with C. pecorum exhibiting a more pronounced recovery of infectious EB production upon subsequent removal of DAMPs from HeLa/Chlamydia culture. Because lysis of host cells during Chlamydia infection, and various other infections, has the potential to markedly increase local concentrations of DAMPs at the site of infection, DAMPs may play a role in the progression of Chlamydia infection in vivo, particularly in the context of poly-microbial infections.

DBMS EXTERNAL SEMINAR NEWS

PLEASE PUT THESE FUTURE DATES ON YOUR PLANNING CALENDAR.

December 2, 2014: Dr. Thirumala-Devi Kanneganti, St. Jude Children’s Research Hospital

Mar 17, 2015: Dr. Arturo Casadevall, Albert Einstein College of Medicine

May 5, 2015: Dr. Ruth Slack, University of Ottawa

More information regarding seminars forthcoming.
Contact Person: Dr. Mike Kruppa
**BIOMEDICAL SCIENCES INTERNAL SEMINAR**

**Eric Beaumont, Ph.D.**
**Associate Professor**

Date: September 26, 2014  
Time: 12:00-1:00 p.m.  
B-06, Building 1  
Quillen College of Medicine/VA Campus

**Chronic autonomic regulation therapy mitigates adverse neuronal remodeling induced by pressure overload**

My recent work has focused on neuronal interactions that occur among the central and peripheral neuronal networks playing a major role in controlling cardiac functions. Imbalances within this control system are associated with heart disease and have deleterious consequences, including the progression into heart failure. Neuromodulation therapy has emerged as a novel approach to treat such disease processes. I am now focusing on the role of vagal nerve stimulation to modulate central aspects of the cardiac control systems, precisely at the level of the Nucleus of the Solitary Tract (NTS).

**Rob Schoborg, Ph.D.**  
**Professor**

Date: October 3, 2014  
Time: 12:00-1:00 p.m.  
B-06, Building 1  
Quillen College of Medicine/VA Campus

**Chlamydia trachomatis: a persistent problem**

The *Chlamydiae* are a genus of Gram-negative, obligate intracellular pathogens that establish infections within mucosal epithelial cells. There are approximately 3 million *C. trachomatis* genital tract infections in the US each year. Up to 70% of infected individuals are asymptomatic and are at increased risk of serious reproductive complications. Once inside a host cell, chlamydiae replicate within a membrane-bound intracellular compartment termed an inclusion. Once they have replicated, chlamydial progeny are released from the inclusion, infect new host cells and spread through host mucosal tissues. In culture, exposure to β-lactam antibiotics (as well as other naturally-occurring stressors) can induce the chlamydiae to leave their normal developmental cycle and enter a non-infectious, non-replicating but viable state termed persistence. Because they are viable, persistent *C. trachomatis* may resume normal development and shed infectious organisms after stressor removal. Persistence has been studied in culture since 1967, but the critical question of whether chlamydiae enter persistence *in vivo* remained unanswered for over 40 years until Regenia Phillips-Campbell, a former Ph.D. student in our laboratory, established the first experimentally-tractable model of amoxicillin-induced *C. muridarum* persistence in mice. We subsequently used this model to demonstrate that persistent chlamydiae are more resistant to azithromycin (AZM) *in vivo*, which suggests that development of persistence may contribute to AZM-treatment failure observed in humans. Hena Yakoob, an undergraduate honors student, recently demonstrated that the anti-Human Immunodeficiency Virus (HIV) drug elvitegravir (EVG) has anti-chlamydial activity. Physiologically-relevant concentrations of EVG reduce production of infectious chlamydiae >90% without inhibiting inclusion formation – an observation that is consistent with persistence induction. Given that >5% of HIV patients are co-infected with *C. trachomatis* at any one time, these observations have significant implications for chlamydial treatment, transmission and disease progression in HIV positive patients receiving EVG. An outline for an R21 proposal to the NIH AIDS and AIDS-Related Program will also be presented in order to acquire pre-submission feedback.
Does (cell) shape matter?

The great diversity of sizes and shapes assumed by different cells of metazoan organisms is something that is well appreciated. However, very little is known about the mechanisms used to produce these shapes, as well as the biochemical signals that elicit them. Very recently, my lab has begun to explore the unique geometrical features of corneal endothelial cells using confocal microscopy in combination with mosaic analysis with double markers (MADM). Our results suggest structure-function relationships that may be integral for these cells to carry out their role as a major determinant of corneal clarity.

Robert Wondergem, Ph.D.
Professor
Date: October 17, 2014
Time: 12:00-1:00 p.m.
B-06, Building 1
Quillen College of Medicine/VA Campus

TRP Ion Channels, Calcium and Glioblastoma Cell Invasion

Synopsis: Transient Receptor Potential ion channels (TRPs) are proving to be the molecular sensors for various stimuli of the peripheral nervous system. None the less, TRPs are showing up in many other cell types, and we know little of their physiologic function in this regard. I will present findings that implicate a role for TRPs in tumor metastasis/invasion, but which may carry over to a range of cellular movements such as those involved in organism/organ development, wound healing and tissue regeneration.

CONGRATULATIONS…

Dr. Eliot Smith has accepted a Post-doctoral position with Dr. Frank Luca at the University of Pennsylvania. He is studying NDR kinases (the animal equivalent of cbk1) and he will be working a lot in zebrafish, over expressing and knocking out NDR kinases in the fish embryos to assess their roles in retina development. A known mutation in dog NDR causes retina degeneration and we want to use zebrafish as a model for eye development (in zebrafish the eye develops in 90 hours!). Dr. Luca’s lab is interested in Yeast and mammalian cell cycle regulation; Regulation of mitotic exit, cytokinesis, daughter cell-specific gene expression, and polarized growth. The Luca lab studies conserved signaling networks that coordinate the diverse cellular processes associated with cell division and cellular morphogenesis. The lab employs multidisciplinary approaches, including yeast genetics, biochemistry and cellular and molecular biology to investigate the conserved functions of the Mob protein family. The budding yeast Saccharomyces cerevisiae expresses two Mob proteins, Mob1 and Mob2, that function in distinct pathways.

Eliot completed his doctoral degree under the guidance of Dr. David Johnson.
http://www.med.upenn.edu/apps/faculty/index.php/g20000220/p1532290.
CONGRATULATIONS...

Dr. Michelle Chandley has accepted a position as Assistant Professor, Department of Health Sciences at East Tennessee State University. Dr. Chandley was a Postdoctoral Fellow in the laboratory of Dr. Gregory Ordway. A drop by reception was held for Michelle on Friday, August 8, 2014.

**Biomedical Sciences Seminar Series Schedule**

All presentations will be at Noon on Fridays and will be in B-06, Stanton-Gerber Hall. Please contact Dr. Brian Rowe at rowe@etsu.edu to schedule a seminar.

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**ALUMNI NEWS**

**Dr. Jingru Sun** was a graduate student in the Biomedical Sciences program at East Tennessee State University from 2004 to 2009. She developed a strong interest in microbial pathogenesis and host-pathogen interactions while working on her PhD dissertation under the guidance of Dr. Robert Schoborg. Her research focused on understanding how *Chlamydia trachomatis*, a Gram-negative obligate intracellular bacterium, alters host cellular functions to replicate and disseminate in the host cells. After receiving her PhD in Biomedical Sciences-Microbiology from ETSU, she joined Dr. Alejandro Aballay’s lab at Duke University Medical Center for postdoctoral training in genetics and neuroscience. She discovered that specific neurons in the nervous system control innate immunity and cellular stress pathways during pathogen infection. In 2014, she was appointed as an Assistant Professor in the College of Medical Sciences at Washington State University. Using *Caenorhabditis elegans* as a model organism, her current research focuses on elucidating the molecular and cellular mechanisms of neuro-immune interactions, such as the activity of specific neurons involved in neural-immune communications, the signal flow between neurons, neural mediators and networks that modulate immune signaling pathways in response to pathogen infection. Jingru currently resides in Spokane, Washington with her husband Ben, who received his Ph.D. from Dr. Yue Zou’s laboratory in the Department of Biomedical Sciences in 2008.

Some of Dr. Sun’s recent papers are listed below:


**Dr. Timothy (Robbie) Southern**, Ph.D., a former PhD student in Dr. Russ Hayman’s laboratory, is promoted to Public Health Laboratory Director for the State of South Dakota. Robbie is currently a Clinical Microbiology Fellow at the University of Nebraska Medical Center and Nebraska Public Health Laboratory. This Fellowship is designed to train laboratory directors and leaders. It has also allowed Dr. Southern to expand his knowledge in Environmental and Forensic Science.

This is a big deal – these positions are very competitive! More importantly, this has been Robbie’s career goal since he started at ETSU about 12 years ago. Cudos to Robbie for his hard work and to Russ for his quality mentorship and training.

(*Source: South Dakota Department of Health newsletter and Dr. Schoborg)*
TURAN TUFAN is a Visiting Scholar, from Adana, Turkey, and is currently employed in the laboratory of Dr. Meng Yang-Zhu. Turan received his MSc. degree in January 2014, from Cukurova University, School of Medicine, Department of Medical Biology and Genetics, Adana, Turkey. His professional training includes employment as a Visiting Researcher at the Agricultural Biotechnology Center, Animal Biotechnology and Stem Cell Institute, Hungary, September-December 2013. His professional experience also includes serving as a trainee at the Immunology Department Hemato-Oncology, as well as the Molecular Biology and Cytogenetic Departments, Diagnosis of Genetic Disease, at the Florence Nightingale Hospital, Istanbul, Turkey.

HEALTH & SAFETY NEWS
All laboratories should always be prepared for the annual inspection conducted by Health & Safety. A few simple reminders:

- Ensure all areas are free of clutter as possible
- Hazardous chemicals stored properly
- All containers need to be labeled to reflect contents
- Flammables and combustible liquids stored in containers labeled as such
- Do not use hood areas for storage
- Do not have food in laboratory areas
- Ensure gas cylinders secured
- Do not block wash stations
- Separate acids and flammables and label doors

Rolf Fritz has a new addition to his farm. This new baby boy Alpaca was born on October 10th. An unexpected and very nice surprise for Rolf. His name is “Butters Dobunni.”

Alpaca have been domesticated for thousands of years. They have been bred mainly for their fiber which is used for knitted and woven items, similar to wool. “Their fleece was cherished by members of the Incan civilization (referred to as “The Fiber of Gods”)”

http://www.ilovealpacas.com/facts.shtml

This cute baby boy resides in the Pleasant Hill Community of Greene County. Hopefully we can have an update in our next newsletter. (Pictures compliments of Rolf Fritz)

CRYSTAL MAUPIN, INFORMATION RESEARCH TECHNICIAN, IS 2ND PLACE WINNER OF THE 2014 ETSU PRIDE CAMPUS DECORATING CONTEST!

MEMORIAL SERVICE HELD FOR ANATOMICAL GIFT DONORS
A Service of Remembrance given by the 1st year students in Medical Human Gross Anatomy was held on Wednesday, October 8, 2014. This is always a special time for the students to honor the donors in the Anatomical Gift program and their contribution in the Medical Human Gross Anatomy & Embryology course.
The effects of antidepressants on DSP4-induced DNA damage response in neuroblastoma SH-SY5Y cells

It has been reported that *locus coeruleus* (LC) degeneration precedes the degeneration of other neurons in the brain in some neurodegenerative diseases, like Alzheimer’s disease (AD) and Parkinson’s disease (PD). The LC contains noradrenergic neurons and is the major source of norepinephrine in the brain. N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP4) has been used widely as a noradrenergic neurotoxin in the development of AD and PD animal models for specific LC degeneration. However, the precise mechanism of action of DSP4 remains unclear. An increase in systemic DNA damage has been found to be related to the pathogenic development of neurodegeneration. Depression symptoms often accompany neurodegenerative disorders. The process of neurodegeneration is not well understood, so current therapeutic approaches are limited to symptomatic relief, such as using antidepressants for depression symptoms. To date, few studies have revealed why different groups of antidepressants have similar clinical effects on relieving depression. This dissertation seeks to provide mechanistic information on DSP4’s selective toxicity to the LC, to correlate this toxicity to aspects of neurodegeneration, and to demonstrate novel, protective features of prescribed antidepressants in ameliorating these effects. The current study demonstrates that DSP4 induces a DNA damage response (DDR) and results in down-regulation of dopamine β-hydroxylase and the norepinephrine transporter, which are noradrenergic phenotypes. DSP4 causes cell cycle arrest in S and G2/M phases, and this arrest is reversible. The current study shows that some antidepressants reduce the DSP4-induced DDR in neuroblastoma SH-SY5Y cells. Flow cytometry data demonstrate that selective antidepressants protect cells from being arrested in S phase. Together, these observations suggest that DSP4 induces DDR, which leads to LC degeneration. In addition, reduction of the DDR is one important pharmacologic characteristic of antidepressants, and may explain why different antidepressants could alleviate depression symptoms in neurodegenerative patients.
HIF-1α IN THE HEART: PROVISION OF ISCHEMIC CARDIOPROTECTION AND REMODELING OF NUCLEOTIDE METABOLISM

In our studies, we found that stabilized expression of HIF-1α in heart led to better recovery of function and less tissue death after 30 minutes of global ischemia. We found that the cardioprotection conferred by HIF is provided by its ability to preserve mitochondrial polarization during ischemic stress. Our group previously showed that the nucleotide metabolic pathway known as the purine nucleotide cycle (PNC) provides fumarate that is used as an alternative terminal electron acceptor to sustain anaerobic mitochondrial respiration. Here, we discovered that HIF-1α stimulates AMP deaminase 2 (AMPD2), the entry point to the PNC. The combination of glycolysis and the PNC may protect the heart's nucleotide resources, thus we examined the effects that HIF-1α exerts on nucleotide metabolism in the ischemic heart. While we found that HIF-1α helps to preserve nucleotides in the ischemic heart we also found that adenosine accumulation in the ischemic heart is attenuated as a result of HIF-1α expression. As ATP is depleted during ischemia, AMP accumulates. Our results suggest that AMP metabolism is shunted towards AMP deaminase rather than the adenosine producing 5'-nucleotidase pathway. Subsequently, we treated hearts with the PNC inhibitor hadacidin followed by 30 minutes of global ischemia. Inclusion of hadacidin reduced ATP and adenylate energy charge in the hearts. These findings allow us to propose that the provision of fumarate by the PNC prevents the F₀F₁ ATP synthase from consuming glycolytic ATP to maintain mitochondrial polarization during ischemia. Thus, the PNC provides ATP sparing effects in the ischemic heart. The fact that ATP and adenylate energy charge is better preserved during ischemia in HIF expressing hearts is supportive of our observation that HIF-1α upregulates the PNC. Finally, we found that HIF-1α induces the expression of the nucleotide salvage enzyme hypoxanthine phosphoribosyl transferase (HPRT). This enzyme may serve to re-incorporate the nucleotide degradation product, hypoxanthine, into the adenine nucleotide pool upon reperfusion and prevent the production of reactive oxygen species in ischemia-reperfusion stress. Collectively, HIF-1α robustly protects the heart from ischemic stress and it induces several metabolic pathways that protect nucleotide resources, which might serve as additional cardioprotective mechanisms.
REGULATION OF C-REACTIVE PROTEIN GENE EXPRESSION AND FUNCTION

Human C-reactive protein (CRP) is the prototypic acute phase protein whose serum concentration increases during inflammatory states, including atherosclerosis. There are two major questions regarding CRP: 1. How is the serum concentration of CRP regulated? 2. What are the functions of CRP in atherosclerosis?

Our first aim was to determine the role of the constitutively expressed transcription factor Oct-1 in regulating CRP gene expression. We found that Oct-1 overexpression inhibited (IL-6+IL-1β)-induced CRP gene expression; maximal inhibition required the binding of Oct-1 to an octamer motif at (-59 to -66) on the CRP promoter. Oct-1 overexpression inhibited both (IL-6+IL-1β)-induced and C/EBPβ-induced CRP gene expression, even when the Oct-1 site was deleted. These findings suggest that Oct-1 is a repressor of CRP gene expression that acts via binding to its cognate site on the CRP promoter, as well as through indirect interactions with other promoter-bound transcription factors.

Our second aim was to investigate the interaction of CRP with oxidized low density lipoprotein (ox-LDL). Acidic pH, a hallmark of atherosclerotic lesions, reversibly alters CRP structure and exposes a hidden binding site that enables CRP to bind ox-LDL. Using site-directed mutagenesis we constructed a CRP mutant (E42Q) that showed significant binding to ox-LDL at physiological pH. E42Q CRP required a less acidic pH for maximal binding, and bound ox-LDL more efficiently than wild type CRP at any pH. We then examined if reactive oxygen species also induced CRP – ox-LDL interaction. H2O2-treated CRP bound ox-LDL at physiological pH. Like acidic pH, H2O2-treatment induced only a local structural change exposing the ox-LDL binding site. E42Q and H2O2-modified CRP are tools to study the function of CRP in animal models of atherosclerosis, which may not have an inflammatory environment sufficient to modify CRP and induce binding to atherogenic ox-LDL.

We conclude that Oct-1 is one of the critical regulators of CRP gene expression, and that CRP can be modified in vitro to convert it into an atherogenic LDL-binding molecule.
Autism spectrum disorder (ASD) now affects one in 68 children in the United States. Disorders within this spectrum share hallmark deficits in verbal and nonverbal communication, repetitive behavior, and social interaction. The cause of ASD is still unknown. Even though hundreds of genetic abnormalities have been identified in ASD, these markers account for less than one percent of all ASD cases. This has lead researchers to continue the search for a more common pathological marker of ASD. Methods used to directly study the ASD brain include brain imaging in living patients and pathology studies using postmortem brain tissues from deceased ASD donors. These methods typically focus on brain regions as a whole with little regard to the underlying cellular complexity. While informative, these approaches do not provide information about the specific brain cells affected and also have not been successful in revealing the underlying cause of ASD. The research presented in this dissertation used innovative methods and a novel approach to investigate the pathology of the ASD brain. This research employed laser capture microdissection to isolate specific cell populations from carefully defined and specific brain regions from ASD and typically developing control brains. These cells were used to interrogate gene expression abnormalities that may underlie biological mechanisms that contribute behavioral abnormalities of ASD. By examining the ASD brain at the level of its most basic component, the cell, I sought to reveal a potentially unifying cellular pathology of the ASD brain that could be used for the development of therapeutic alternatives for ASD patients.
Abstract

Pre-infection of BALB/c mice with Chlamydia muridarum protects mice from subsequent Herpes Simplex Virus challenge

Slade, Jessica, Hall, Jennifer V., Kintner, Jennifer, and Robert Schoborg, Department of Biomedical Sciences, Center for Innate Immunity, Infectious Disease and Immunity, Quillen College of Medicine, East Tennessee State University, Johnson City, TN

Chlamydia trachomatis and Herpes Simplex Virus-2 (HSV-2) are the leading bacterial and 2nd leading viral cause of human sexually transmitted infections, respectively. Co-infection with C. trachomatis and HSV-2 has been reported in humans and studied in vitro but the clinical consequences are unknown. We hypothesized that disease progression and/or pathogen shedding in co-infected mice would differ from that in singly-infected mice. BALB/c mice were vaginally co-infected using 3 scenarios: i) infection with $10^6$ IFU C. muridarum (Cm) followed 3 days later by $5 \times 10^3$ PFU HSV-2 (Cm-3D-H3); ii) infection with HSV-2 followed 3 days later by C. muridarum (H3-3D-Cm); or iii) simultaneous infection with a combined inoculum of C. muridarum and HSV-2 (Cm+H3). Mock, C. muridarum, and HSV-2 singly-infected mice served as controls. Mice singly-infected with HSV-2 exhibit viral shedding and 75% mortality, but Cm-3D-H3 and Cm+H mice exhibit reduced viral shedding and 0% and 8% mortality, respectively. H3-3D-Cm mice exhibit mortality and viral shedding similar to that observed with HSV-2 singly-infected mice. These data suggest that chlamydial pre-infection protects mice from HSV-2-induced death. To further understand the protective effect elicited by chlamydial pre-infection, we investigated whether this effect required viable chlamydiae by infecting with UV-irradiated C. muridarum on day 0 (D0) then with HSV-2 on D3 (UVCm-H3) and by curing Chlamydia-infected mice with azithromycin (AZM) on D6 followed by HSV-2 infection on D9. UVCm-H3 mice exhibit intermediate protection, whereas mice treated with AZM exhibit mortality similar to HSV-2 singly-infected mice. These data indicate that non-viable chlamydiae present in the genital tract at the time of HSV-2 infection can provide some protection from HSV-2-induced neuropathology, but that actively-replicating chlamydiae are required for full protection. To determine how long the protective effect lasts, mice were infected with C. muridarum on D0 then with HSV-2 on D9 or D27. D9 co-infected mice still exhibit 0% mortality, but by D27, when viable chlamydiae are no longer detected in the genital tract, protection is not observed. Thus, Chlamydia-induced protection is transient and likely requires the presence of chlamydiae or their components. These data demonstrate that chlamydial pre-infection can alter progression of subsequent HSV infection, with significant implications for HSV transmission from co-infected humans.
# 2015 COMMITTEE MEMBERS

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<th>Promotion and Tenure Committee FY 2015</th>
<th>Research and Mentoring Standing Committee</th>
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<td>Gregory Ordway</td>
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<td>Brian Rowe</td>
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<td>Brian Rowe – Internal Seminars</td>
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<td>Cindy Canter - Staff</td>
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College of Medicine Committee Membership

**Admissions Committee**
Dave Johnson (2016)
Greg Ordway (2017)
Antonio Rusinol (2015)
Krishna Singh (2015)
Tom Kwagiroch – ex officio

**Dean's Administrative Council Committee**
Theo Hagg

**Diversity Council**
Antonio Rusinol – Chair

**Faculty Advisory**
Gary Wright – Secretary (2016)
Eric Beaumont (2017)
Donald Hoover (2017)
Yue Zou (2017)
Paul Monaco (2017)

**Financial Aid and Scholarship Committee**
Tom Kwagiroch – Chair, ex-officio
Paul Monaco (2015)
Brian Rowe (2014)

**Committee on Gender and Special Issues**
Michelle Duffourc (2013)
Theresa Harrison (2015)
David Johnson (2015)
Tom Kwagiroch – ex-officio

**College Leadership Group**
Theo Hagg – ex officio
Tom Kwagiroch – ex officio
Mitch Robinson – ex officio

**Learning Resources Advisory Committee**
Phil Musich – Chair (2016)
Tom Ecay (2016)

**Promotion and Tenure Committee**
Dennis Defoe (2016)
Tom Ecay (2016)
Robert Wondergem (2015)
Meng-Yang Zhu (2016)

**MSEC Committee**
Voting:
Michelle Duffourc
Jennifer Hall
Dave Johnson
Paul Monaco

Non Voting:
Tom Kwagiroch

**Outcomes Subcommittee:**
Paul Monaco

**Nutrition Working Group:**
Tom Ecay - Chair

**M1/M2 Review Subcommittee:**
Dave Johnson - Chair
Michelle Duffourc
Antonio Rusinol
Rob Schoborg

**M3/M4 Review Subcommittee:**
Russ Hayman

**Integrated Ground Rounds Working Group:**
Rob Schoborg – Co-Chair
Michelle Duffourc
Tom Ecay
Russ Hayman

**Student Promotion Committee**
Michelle Duffourc
Tom Ecay
Russ Hayman
Paul Monaco
Mitch Robinson
Tom Kwagiroch – ex officio