Dear Colleagues

The last half year has been a bit of a roller-coaster of emotions for our Department. We started off with a wonderful Holiday Party at the Blackthorn Club, thanks to Dr. Kwasigroch, with the excellent assistance of Cindy Canter, Robin Montgomery and Cynthia Taylor. Many people commented on the great food, excellent venue and, most importantly, the palpable team spirit of the Department. We were especially appreciative of Dr. Means and his wife for joining us. We also were grateful that we had a chance to talk with TJ Neal who was recovering from having been in hospital with a critical illness. All in all, the evening was a success, as also judged by the many who showed their smooth moves on the dance floor. The polka definitely was one of the highlights of the evening.

Soon afterwards we learned that Dr. Schambra and Dr. Wondergem were hospitalized with serious life-threatening conditions. In particular, Dr. Wondergem’s miraculous recovery truly taught us the precious nature of life. The response by the members of the Department and others in the College of Medicine revealed that we are united in our compassion and care for each other. It is a blessing for me to be part of this group. We do wish both of them endurance, patience and joy in their continued recovery.

I would like to highlight and commend Drs. Ecay and Rowe for keeping the Physiology course on track despite the sudden need to fill in for Dr. Wondergem. Others in the Medical and Graduate Student courses also continue to be highly successful. A special thanks goes out to the Course Director group (Abercrombie, Beaumont, Duffourc, Ecay, Hayman, Kwasigroch, Monaco, Robinson, Schoborg) who I have had the privilege to work with for over more than a year. Their commitment to the students and our department is remarkable. We have already received excellent feedback from our students. The academic year end is in sight and I am sure many of you are looking forward to a well-deserved period of rest during your summer vacation.

We celebrated the December graduation of Jessica Crawford, Avinash Thirumalai, Yan Wang and Joe Wu. Congratulations to them and their supervisors, Drs. Ordway, Agrawal, Zhu and Wright on achieving this milestone. They looked real spiffy in their academic gowns walking across the podium at Commencement. I also would like to extend congratulations...
to Suman Dalal who successfully defended her PhD thesis in India in March 2015. We welcomed several new graduate students in the DBMS laboratories. It is a privilege to be involved in their training.

We welcomed two superb scientists to our department for our External Seminar series, Dr. Jim Geddes from the University of Kentucky and Dr. Thirumala-Devi Kanneganti from St. Jude’s. This flagship series exposes us to fascinating research and fosters collaborations. It also helps to increase our visibility among our colleagues at other Institutions. We continued to hear excellent seminars through our Internal Seminar series, and to discuss many outstanding publications in our Journal club. These have led to new ideas and collaborations and I highly recommend attending the seminars and journal club meetings. I very much appreciate all the work by Drs. Zou, Rowe and Campbell that goes into organizing these programs.

I am excited to be part of a recruitment drive for four Faculty positions in which we are hoping to attract new colleagues who can join us in our mission. After an initial phone interview in December and January, and an in person interview in February and March, we now have a pool of excellent candidates. Several of them have indicated that we are their top pick from among several Institutions. A special thanks goes out to everyone who participated in this major undertaking, especially Mary Lou, as well as the Faculty Recruitment Committee (Agrawal (Chair), Beaumont, Palau, Schoborg, Singh, Wondergem and Zhu). Several DBMS members braved the weather during the storms, some of them even walked in. Your efforts definitely made an impact. All of the candidates commented on the extremely friendly reception they received and the quality of our department as a whole. I want to thank each and every one of you for your help and commitment to the future of the Department of Biomedical Sciences. The colleagues who will join us in the Summer and Fall will become part of a great team. I believe that our efforts and accomplishments this year will twenty years from now be seen as having contributed to one of the important events in the history and development of the department. Again, please accept my most sincere thanks for a job well-done.

Group picture of the Department of Biomedical Sciences. Many thanks to Mr. Gerry Philpott, Photographer, for this picturesque photo taken in the Fall of 2014. Photo was taken on the pristine VA Campus utilizing the beautiful Buffalo Mountains as a scenic backdrop. Also, many thanks to Ms. Tonya Ward, for her role in organizing and coordinating this event. Buffalo Mountain consists of 725 acres of natural preserve with many hiking trails—one of the many natural wonders of Northeast Tennessee.
Extended winter weather resulted in an unprecedented 4-day suspension, from February 16 through February 19, for the campus of East Tennessee State University. Heavy snows coupled with sub degree temperatures played havoc on Tennessee causing a week-long cancellation of schools and universities throughout the Tri-Cities area and Northeast Tennessee. Extremely cold temperatures, snow, ice, freezing rain and sleet kept most folks off the roads and confined inside. ETSU employees and students returning to work and school on February 20th at 10:00 a.m. were still confronted with ice and snow-covered walkways and grounds, coupled with temperatures of greater than -10 degrees in most of the area. In addition, 6-7” of additional snow covered the Tri Cities the following week that resulted in additional closings for the University. No doubt this will be a winter to remember! (Pictures of winter scene on VA Campus compliments of TJ Neal)

For those that believe in folklore, Punxsutawney Phil (pictured above) predicted six more weeks of bad weather. “Groundhog Day is a day celebrated on February 2. According to folklore, if it is cloudy when a groundhog emerges from its burrow on this day, then spring will come early; if it is sunny, the groundhog will supposedly see its shadow and retreat back into its burrow, and the winter weather will persist for six more weeks.” (Wikipedia)
RECENT JOURNAL PUBLICATIONS


SCIENTIFIC MEETINGS/INVITED SEMINAR PRESENTATIONS

Dr. Alok Agrawal, Professor, was invited to present a seminar at the Twinbrook Immunology Interest Group Seminar Series, NIH National Institute of Allergy and Infectious Diseases, on January 27, 2015. The campus is located in Rockville, MD. The seminar was entitled “Mechanisms of Host-Defense Functions of C-reactive Protein.”

Heath Nier presented a paper entitled, “Improved Method of VNS Therapy Titration that Reduces Time to Achieve Target VNS Intensity and Reduces Severity of Stimulation-related Side Effects,” at the North American Neuromodulation Society meeting (Dec 1 to 14, 2014) in Las Vegas NV. This work is 100% supported by the Cyberonics grant to ETSU and Dr. Jeff Ardell.

Dr. Rob Schoborg, Dr. Jennifer Hall, Jessica Slade (Graduate Student) attended the Chlamydia Basic Research Society meeting to be held in New Orleans March 29-April 1, 2015. Dr. Hall will be giving an oral presentation of the abstract, “Progesterone antagonizes estrogen-stimulated enhancement of Chlamydia trachomatis serovar E infection in genital epithelial cell/stromal cell co-culture.” Jessica Slade will present a poster for her abstract, “Pre-infection of BALB/c mice with Chlamydia muridarum protects mice from subsequent Herpes Simplex Virus challenge.”

Dr. Theo Hagg and Dr. Cuihong Jia, attended the Society for Neuroscience meeting held in Washington, DC, November 15-19, 2014.

STUDENT GRANT AWARDS—CONGRATULATIONS!

Melissa Eggert, a second-year medical student at the Quillen College of Medicine, was awarded $1,000 through the ETSU Behringer Interprofessional Education Scholarship Program. Ms. Eggert was sponsored by Dr. Caroline Abercrombie, Assistant Professor at the medical school and Adjunct Faculty, Department of Biomedical Sciences, The award will be used to purchase supplies for health screenings at the Johnson City Farmers Market. Eggert’s “Community Nutritional Health Outreach” project will include involvement from students in the colleges of medicine, pharmacy and clinical and rehabilitative health sciences.

Mahon Mahmodian and Benjamin Jewett, Honors Students working in the Laboratory of Dr. Gregory Ordway, were awarded a Student-Faculty Collaborative Grants administered by the ETSU Honors College, in the amount of $1000 each. The project completion date for the students is June 2015. This award is particularly noteworthy because there was a large and high quality pool of proposals submitted.

COMMITTEES AND MEMBERSHIPS

Dr. Alok Agrawal, Professor, served on the “Innate Immunity and Inflammation” Study Section Review Committee, NIH, February 12-13, 2015, which was held in Arlington, VA.

Dr. Ken Ferslew, Professor, has been selected to serve as a member of the Chemistry/Instrumental Analysis Scientific Area Committee’s (SAC’s) Toxicology Subcommittee within the Organization of Scientific Area Committees (OSAC). The appointment is nominally a 3-year term. Committee charge and purpose is to “strengthen the nation’s use of forensic science by supporting the development and promulgation of forensic science consensus documentary standards and guidelines.” The Committee is a division of the United State Department of Commerce, National Institute of Standards and Technology.
Dr. Kenneth Ferslew, Professor, gains recognition for his contributions to the field of forensic toxicology. Dr. Ferslew has been a Faculty Member and Director of the W. L. Jenkins Forensic Center at the College of Medicine for the past 32 years.

Recently Dr. Ferslew has authored two chapters included in the Sixth Edition of Garriott’s Medicolegal Aspects of Alcohol, published in October 2014 by Lawyers & Judges Publishing Company, Inc. This newest edition provides updated scientific studies and information on many complex topics relative to medicolegal aspects of alcohol. It contains a wealth of sound scientific information, support, and aid that can be drawn upon as needed by researchers as well as litigators. Dr. Ferslew was recently featured in the December 7, 2014 issue of the Elizabethton Star, and the December 2014 issue of the ETSU ACCENT.


Dr. Michelle Chandley, Assistant Professor at East Tennessee State University, Department of Health Sciences, and Dr. Gregory Ordway, Professor Department of Biomedical Sciences, co-author book chapter on depression and suicide. The First Edition of A Concise Guide to Understanding Suicide: Epidemiology, Pathophysiology and Prevention, contains a chapter co-authored by Chandley and Ordway entitled, “The noradrenergic system in depression and suicide.” Collaboration by Drs. Ordway and Chandley was supported by Grants from the American Foundation for Suicide Prevention (Grants from NIMH: MH46692 that was funded from 1991 to 2014, MH02031, MH63187, and MH58211). Dr. Chandley received her doctoral degree in Biomedical Sciences at the Quillen College of Medicine and Postdoctoral training in the laboratory of Dr. Gregory Ordway.

Book Overview: “This text will educate practicing clinicians, (psychologist, psychiatrists, nurses, counselors, and emergency room personal) and other health care workers and researchers, as well as providing a pathway for undergraduate and graduate students interested in furthering their understanding of the complexities surrounding suicide. Further, the mental health professionals and those in the social sciences will be extremely interested in this monograph, as will the University community, armed forces and interested lay public.”

Dr. Hoover Recognized for Nervous System Research

The December issue of ETSU Accent acknowledged Dr. Don Hoover for his contribution to research and for being the recipient of a grant through the National Institute of Health. This three-year grant in the amount of $337,400, will allow Dr. Hoover and Co-Investigator, Dr. Tammy Ozment, Research Assistant Professor, Department of Surgery, to conduct research on the nervous system’s interaction with the spleen in restraining inflammatory responses and how this feedback system works. By doing so, they hope to see if there is a therapeutic advantage particularly relative to sepsis. Sepsis is a very serious and life-threatening complication of an infection. According to Dr. Hoover, “Almost one million people get sepsis per year in the United States. Twenty-five percent of those with severe sepsis die and the survivors have a lot of residual problems.”

Dr. Palau Recognized for Contributions to Cancer Research

Dr. Victoria Palau, Associate Professor, Bill Gatton College of Pharmacy, and Adjunct Faculty-Department of Biomedical Sciences, was recently featured in the Elizabethton Star for her contributions to cancer research. Dr. Palau’s research focus is upon identifying and testing various plant-derived compounds and their impact on various types of cancer. This has been her life’s work for the last seven years and she plans to continue her quest in hopes of identifying those compounds that will lead to better cancer treatments.

2014 SERVICE AWARDEES

<table>
<thead>
<tr>
<th>Name</th>
<th>Years of Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas E. Kwasigroch</td>
<td>35</td>
</tr>
<tr>
<td>Judy Ann Whittimore</td>
<td>35</td>
</tr>
<tr>
<td>William L. Joyner</td>
<td>25</td>
</tr>
<tr>
<td>Robert V. Schoborg</td>
<td>25</td>
</tr>
<tr>
<td>Jennifer Kintner</td>
<td>10</td>
</tr>
<tr>
<td>Gary Leslie Wright</td>
<td>5</td>
</tr>
</tbody>
</table>

DBMS EXTERNAL SEMINAR NEWS

Please put these future dates on your planning calendar.

April 14, 2015: Thomas Huckaba, PhD, Assistant Professor of Biology, Xavier University of Louisiana, New Orleans, LA

May 11, 2015: Rick Lin, PhD, Professor, University of Mississippi Medical Center, Jackson, MS

More information regarding seminars forthcoming.

Contact Person: Dr. Mike Kruppa
Welcome… Matthew P. Keasey, PhD, Visiting Scholar

Dr. Keasey is originally from Sedgley in the United Kingdom and will be working for the next six months in the laboratory of Dr. Theo Hagg to help complete a long-term and an ongoing study. The current study is based on understanding the signaling mechanisms that underpin integrin mediated expression of Leukemia Inhibitory Factor.

Dr. Keasey completed his Ph.D. at the University of Bristol, UK in 2010 before spending two years as a postdoctoral fellow at the University of Louisville, KY, and a further two years at the Federal University of Pernambuco, Brazil.

Recent publications include the following:


Welcome… Lylyan F. Pimentel, Visiting Scholar

Ms. Pimentel is a Visiting Scholar who will be assisting Dr. Keasey and Dr. Theo Hagg’s laboratory for the next six months to complete an ongoing project. She is a resident of Jardim São Paulo, Brazil. She holds a Masters of Science Degree in Biological Science with a concentration in Molecular Biology from the Universidade Federal De Perambuco, Brazil, and is currently working on her Ph.D. in Neuroscience. Recent publications include the following:


Welcome… Hannah Malone, Research Assistant

Hannah graduated from ETSU in May 2014, with a B.S. in Microbiology (graduated top 4 of her concentration). As an undergraduate intern she worked in the Gross Anatomy lab at Quillen College of Medicine. During this time she helped to facilitate the first neuroanatomy lab course for second year medical students. Currently she is employed as a temporary research assistant in the laboratory of Dr. Theo Hagg. Her duties include microsurgery, histology, as well as image analyses. In addition, she assists in or performs basic molecular biology or tissue culture. Hannah is a resident of Jonesborough, TN, and graduate of David Crockett High School. Always having a great interest in the medical and science fields, her long-term goal is to eventually enter into an MD/PhD program.
Welcome... Nishant P. Visavadiya, PhD, Research Associate

Dr. Visavadiya has joined the laboratory of Dr. Theo Hagg as Research Associate, effective March 9, 2015. He holds a Ph.D. degree from the Sardar Patel University, India, with a concentration in Zoology. He furthered his training as Postdoctoral Scholar at the Spinal Cord and Brain Injury Research Center (SCoBIRC), University of Kentucky (2008-2014). And, in 2014, he was appointed to the position of Scientist II at the Spinal Cord and Brain Injury Research Center (SCoBIRC) University of Kentucky. His scientific focus and research interests include the study of redox biology, principally; the redox-mediated cellular mechanisms involved in various chronic pathophysiological diseases with potential therapeutic targets that can participate in redox homeostatic and signaling mechanisms. Recent publications include the following:

*Co-first authorship.


Welcome... Kalpita Banerjee, PhD, Research Associate

Dr. Banerjee joins the laboratory of Dr. Theo Hagg as Research Associate, effective April 6, 2014. Dr. Banerjee holds a Ph.D. degree from Calcutta University, Kolkata, India, with a concentration in Neuroscience. She completed her Postdoctoral training at Burke-Cornell Medical Research Institute, Cornell University, NY (2005-2011). She continued her professional training as Postdoctoral Research Scholar, Burke-Cornell Medical Research Institute, Weill Cornell Medical College.

Her scientific focus and research interests on Parkinson's disease and aging, mainly on the effect of alpha synuclein and dopamine on mitochondria and its consequences in cell death. Postdoctoral training is also in neurodegenerative diseases with special emphasis on Alzheimer's diseases and its relation with mitochondrial stress, protein transport, autophagy/mitophagy and cell death. Recent publications include the following:


HOLIDAY GATHERING 2014
On January 2, 2014, we officially welcomed our new Departmental Chair, Dr. Theo Hagg. After a year of new leadership changes, and new challenges, the Department of Biomedical Sciences held its annual holiday gathering on December 18, 2014, at the Blackthorn Country Club in Jonesborough, TN. This event was a nice ending to the year and summed up the first year for Dr. Hagg’s leadership, and the many successes and accomplishments for the department. Dr. Hagg extended many thanks and credit to the faculty and staff for their continued support and dedication to the Department.  (Photos compliments of Tonya Ward and Jessica Crawford)

CORE FACILITY HOSTS OPEN HOUSE
The Department of Biomedical Sciences Microscopy Core Facility hosted an OPEN HOUSE event on November 20, 2014. This event gave faculty, staff, and students an opportunity to see the new Leica TCS SP8 confocal microscope, tour the facilities, and meet the core facility staff. Many thanks are extended to Dr. Don Hoover and Staff for organizing this event.

PLANS ARE CURRENTLY UNDERWAY FOR A SUMMER “PIG OUT” BARBEQUE FOR THE DEPARTMENT OF BIOMEDICAL SCIENCES. ANGELA THOMPSON AND CRYSTAL MAUPIN ARE COORDINATING THIS EVENT. KEEP YOUR “PEEPERS” OPEN FOR A DATE FORTHCOMING SOON!

APPALACHIAN STUDENT RESEARCH FORUM AND BOLAND SYMPOSIUM
April 8-9 2015
ETSU Culp Center
CONGRATULATIONS TO OUR RECENT GRADUATES

Avinash Thirumalai, PhD
Currently seeking postdoctoral position.

Joe Wu, PhD
Postdoctoral Trainee
Molecular and Applied Nutrition Training Program
Department of Nutritional Sciences
University of Wisconsin
Madison, WI

Yan Wang, PhD
Immunology Track
Department of Population Health and Pathobiology
North Carolina State University
Raleigh, NC

Jessica Crawford, PhD
Research Associate
Department of Biomedical Sciences
Quillen College of Medicine
Johnson City, TN

Christopher Daniels, PhD
Associate Director-Clinical Labs
Medscape, A Global CRO
Cincinnati, OH

Joe Wu, PhD
Postdoctoral Trainee
Molecular and Applied Nutrition Training Program
Department of Nutritional Sciences
University of Wisconsin
Madison, WI
Role of Ataxia Telangiectasia Mutated Kinase in the Healing Process of the Heart Following Myocardial Infarction

Ataxia telangiectasia (AT), caused by the mutations in the gene encoding ataxia telangiectasia mutated kinase (ATM), is a rare autosomal recessive disorder. AT individuals exhibit neuronal degeneration, and are predisposed to cancer. Carriers of this disorder are predisposed to cancer and ischemic heart disease. Heart disease, mostly due to myocardial infarction (MI), is a leading cause of death in the US. Following MI, release of catecholamines in the heart stimulates β-adrenergic receptors (β-AR). Our lab has shown that β-AR stimulation increases ATM expression in the heart and myocytes, and ATM plays an important role in β-AR-stimulated myocardial remodeling with effects on function, fibrosis and apoptosis. Using wild-type (WT) and ATM heterozygous knockout (hKO) mice, this study investigated the role of ATM in the inflammatory, proliferative and maturation phases of infarct healing post-MI. During the inflammatory phase, 1 and 3 days post-MI, deficiency of ATM resulted in decreased left ventricular dilation as measured by echocardiography. It decreased the number of neutrophils and macrophages in the heart 1 day post-MI. Myocardial fibrosis, expression of alpha-smooth muscle actin (α-sma) and apoptosis were higher in the infarct region of ATM deficient hearts. Akt activation (anti-apoptotic) was lower, while Bax expression (pro-apoptotic) was higher in the infarct region of ATM deficient hearts. During the proliferative phase, 7 days post-MI, ATM deficiency attenuated cardiac dysfunction as measured by echocardiography. ATM deficient hearts exhibited increased fibrosis and expression of α-sma in the infarct region with increased myocyte apoptosis in the border area. During the maturation phase, 14 and 28 days post-MI, ATM deficiency resulted in exaggerated cardiac dysfunction. It associated with increased fibrosis, expression of α-sma and decreased cardiac cell apoptosis in the infarct region 28 days post-MI. Myocyte hypertrophy was greater in the non-infarct region during ATM deficiency. ATM deficiency decreased expression of p16 (marker of cell senescence) and activation of pro-apoptotic protein, GSK-3β. Thus ATM modulates the remodeling processes of the heart, including function, fibrosis, apoptosis and hypertrophy post-MI. It - 1) delays inflammatory response acute post-MI; 2) decreases dilative remodeling during inflammatory and proliferative phases; 3) exaggerates cardiac dysfunction during the maturation phase.
BIOMEDICAL SCIENCES EXTERNAL SEMINAR SPEAKERS

James W. Geddes, PhD
Director and Professor
Spinal Cord and Brain Injury Research Center
Admiral William Sheeley Chair in Spinal Cord & Head Injury
University of Kentucky, Lexington, KY
*Why so many calpains? Roles of typical and atypical calpains in the CNS*
Date: November 10, 2014

Thirumala-Devi Kanneganti, PhD
Member, St. Jude Faculty
St. Jude’s Children’s Research Hospital
Memphis, TN
*IL-1 Regulation in Inflammatory Disease*
Date: December 2, 2014

Nishant Visavadiya, PhD
Scientist II
Spinal Cord & Brain Injury Research Center
University of Kentucky, Lexington, KY
*Role of Mitochondria-Associated Secondary Injury Events in Neurotrauma*
Date: January 23, 2015

Kalpita Banerjee, PhD
Postdoctoral Researcher
Burke-Cornell Medical Research Institute
Cornell University
*Neurodegenerative disease & mitochondrial protein and signaling*
Date: February 6, 2015
BIOMEDICAL SCIENCES INTERNAL SEMINAR SPEAKERS

Sharon Campbell, PhD
Assistant Professor
Department of Biomedical Sciences
Title: To E or not to E?
Vitamin E isoforms as therapeutics and preventatives for colon cancer
Date: November 7, 2014

Meng-Yang Zhu, PhD
Professor
Department of Biomedical Sciences
Title: A genetic strategy to restore impaired noradrenergic function by increasing expression of noradrenergic phenotypes in the locus coeruleus in Parkinson’s disease model mice
Date: November 14, 2014

Tom Ecay, PhD
Professor
Department of Biomedical Sciences
Title: The Ins and Outs of Calcium Accumulation during Embryonic Development
Date: November 21, 2014

Deling Yin, MD, PhD
Professor
Department of Internal Medicine
Regulation of IL-10 Mediated Signaling by Toll-Like Receptors and β-Arrestins
Date: February 13, 2015

Michael Kruppa, PhD
Assistant Professor
Department of Biomedical Sciences
Everything you wanted to know about Candida albicans ...but were afraid to ask
Date: March 6, 2015

Gary Wright, PhD
Associate Professor
Department of Biomedical Sciences
O₂-sensory induced cytoprotective mechanisms
Date: March 27, 2015
William Jewett in Johnson City is a long-time member of Bacchus; my son-in-law Jason Pyle has been a member for about 5 years. Through their efforts, places were arranged for me and all 5 of my sons (Rich, Joe, Tom, John, Frank) on their float, “1001 Arabian Nights” in the themed Bacchus parade “Children’s Stories That Live Forever”. The parade rolled on Sunday Feb. 15 during Mardi Gras in New Orleans. Altogether, we comprised ten of about 30 riders on the float. Most of the wives accompanied us, along with 3 of my daughters (Krystyna, Roseanna, Monica), grandchildren; and nephews from my home state, New Jersey.

The Mardi Gras tradition is for parades with floats, marchers, and bands - starting 2 weeks before Mardi Gras (translation, Fat Tuesday), with the objective being for lively partying before start of the Lenten Season which begins at Midnight of Fat Tuesday (Feb 17, this year). People attend parades for the fanfare and to catch ‘throws’ (beads, trinkets, stuffed animals, illuminated objects, etc) from float riders. Fun is had by all.

The parade ends inside the New Orleans Convention Center, with all of the parade, including floats, riding through the ballroom with riders’ guests in formal attire. The party continues to 4am when the band stops playing.

Because I had positions at Tulane and LSU in the 1970s, my older children experienced Mardi Gras as youngsters; after moving to ETSU, we still made periodic trips to Mardi Gras, so my younger children also know the traditions. This latest trip turned out to be a family reunion with all of us getting together in daylight in the French Quarter for cajun and creole food; and street parties. Night time was spent watching other parades. We hope to repeat this.

Our resident “Mad Scientist” (Dr. Theo Hagg), and “Effie Trinket” from The Hunger Games” (Crystal Maupin) added some Halloween Spirit to the Department.
Progesterone antagonizes estrogen-stimulated enhancement of *Chlamydia trachomatis* serovar E infection in genital epithelial cell/stromal cell co-culture.

Jennifer Kintner, Priscilla B. Wyrick, Robert V. Schoborg and Jennifer Hall

**Background and Significance:** Estrogen and progesterone regulate the female menstrual cycle. Studies indicate progesterone can be agonistic or antagonistic to *C. trachomatis* (*Ct*) infection. Estrogen enhances chlamydial infection through uncharacterized mechanisms. Data from an endometrial epithelial cell (Ishikawa, IK)/stromal cell (SHT-290) co-culture model indicate that estrogen-stimulated stromal cell effectors (SCE) indirectly aid chlamydial development in IK cells. Additionally, estrogen-exposed stromal cells secrete increased osteopontin (OPN) and vimentin (VIM), and reduced fibronectin (FBN), suggesting a role for these proteins in modulation of chlamydial infection. **Objectives:** 1) Determine if the SCE osteopontin, vimentin, or fibronectin modulate *Ct* infection in estrogen-exposed IK cells. 2) Determine if progesterone prevents enhancement of *Ct* infection in estrogen-exposed IK/SHT-290 co-cultures. **Methods:** *Ct*-infected IK monolayers were exposed to estrogen +/- recombinant (r) FBN, VIM, or OPN. *Ct*-infected IK or IK/SHT-290 cultures were exposed to medium containing estrogen or progesterone alone or in combination. At 48hpi, samples were collected from each experiment for analysis of inclusion development by infectivity assay and EB progeny production by subpassage. **Results:** Inclusion formation increased with estrogen+rVIM or rOPN exposure while estrogen+rFBN decreased inclusion formation compared to estrogen alone. Estrogen+rOPN exposure caused a significant increase in EB production compared to estrogen alone. Progesterone alone or in combination with estrogen decreased inclusion formation and EB production compared to estrogen alone. **Conclusions:** Together, estrogen and SCE modulate chlamydial development; osteopontin and/or vimentin enhance infection, whereas fibronectin reduces infection. Progesterone negatively affects chlamydial development and antagonizes estrogen-stimulated enhancement of *C. trachomatis* in IK/SHT-290 co-culture.

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

Jessica Slade, Jennifer Hall, Jennifer Kintner and Robert Schoborg

**Background and Significance:** Co-infection with *Chlamydia trachomatis* and Herpes Simplex Virus -2 (HSV-2) has been reported in humans and studied *in vitro*, but the clinical consequences are unknown. **Objectives:** To determine whether disease progression and/or pathogen shedding differs between *C. muridarum* and HSV-2 singly-infected versus co-infected animals. **Methods:** Female BALB/c mice were vaginally co-infected with $10^6$ IFU *C. muridarum* (*Cmur*) followed 3, 9 or 27 days later by $5 \times 10^3$ PFU HSV-2. Alternatively, viable chlamydiae were replaced with $10^6$ IFU UV-irradiated *Cmur* or azithromycin-cured from the genital tract (GT) before HSV-2 co-infection. *Cmur* and HSV-2 singly-infected mice served as controls. Vaginal swabs were performed to determine pathogen shedding by chlamydial titer assay and viral plaque assay. HSV-2-induced morbidity and mortality was monitored daily.
Results: Compared to HSV-2 singly-infected controls, infection with Cmur 3 or 9 days prior to HSV-2 co-infection conferred significant protection from HSV-2-induced disease and reduced viral shedding. Protection against mortality was not observed when: i) mice were co-infected with HSV-2 27 days post Cmur infection; ii) mice were co-infected with UV-irradiated Cmur and HSV-2 or; iii) Cmur-infected mice were azithromycin-treated before HSV-2 co-infection. Conclusions: Protection from HSV-2-induced disease is observed when Cmur is detectable in the GT prior to HSV-2 infection, but is not observed when Cmur-infected mice are no longer shedding detectable chlamydiae either naturally or due to antibiotic treatment. These data suggest that viable chlamydiae must be present in the GT at the time of HSV-2 infection to protect from HSV-2-induced disease.

Improved method of VNS therapy titration that reduces time to achieve target VNS intensity and reduces severity of stimulation-related side effects

Heath Nier, E. Marie Sutherland, Imad Libbus, Badri Amurthur, Bruce H. KenKnight, Jeffrey L. Ardell

Background: VNS Therapy for treatment-resistant epilepsy has been shown to reduce seizure burden, and seizure burden reduction may be related to programmed VNS parameters, including maximum tolerable intensity. Following implantation and activation of VNS Therapy, intensity (pulse frequency, width and amplitude) is limited by side effects, such as cough, encountered at the tolerance zone boundary (TZB). Over time, TZB increases and side effects subside. However, TZB evolution is highly dependent on VNS parameters. We sought to determine whether a new VNS titration method resulted in more rapid elevation of TZB, thereby reducing the time required to achieve therapeutic levels of VNS intensity. Methods: 8 adult canines received VNS Therapy system implant (Cyberonics, Houston, TX) involving the left cervical vagus nerve. Subjects were randomized to titration Group A (traditional titration) or Group B (rapid titration). VNS parameters were adjusted during weekly titration sessions (conscious, unanesthetized) to determine the severity of side effects encountered at the TZB (grade 0 (no effects) to 3 (very severe)). Group A were stimulated throughout the entire titration period using default VNS parameters: 30 Hz pulse frequency, 500 µsec pulse width, 30 sec-ON and 5 min-OFF (262 cycles/day). Current amplitude was adjusted during each titration session to determine TZB. Group B were stimulated using different initial parameters; 10 Hz pulse frequency, 130 µsec pulse width, 14 sec-ON and 1.1 min-OFF (1080 cycles/day) that have been previously shown to promote rapid adaptation. In Group B, pulse width and frequency were increased to ³ 250 µsec and ³ 20 Hz as accommodation to VNS intensity spontaneously improved during the titration period. To eliminate side effect exposure between weekly titration sessions, current amplitude was programmed to a level that elicited no side effects. Results and Conclusions: After completing 9 titration sessions over 8 weeks, tolerable VNS current amplitude was 370% higher (p<0.05) and TZB side effect severity was lower in Group B [2.6±0.3 mA, 0-1 (none-mild)] compared to Group A [0.7±0.3 mA, 2-3 (moderate-severe)]. The mechanisms underlying the more favorable outcomes in Group B may be related to frequency-dependent recruitment of central neural processing of expiratory reflex (cough), selective recruitment of afferent vagus nerve fibers that promote reflex accommodation, and more frequent cycling at higher duty cycle. The Group B methodology (rapid titration) should be evaluated in de novo VNS Therapy patients and in patients for whom the TZB has not increased to levels consistent with expected therapeutic outcomes.