MUSC
DEPARTMENT of PATHOLOGY & LABORATORY MEDICINE

PATHOLOGY & LABORATORY MEDICINE NEWSLETTER

Volume 2, Issue 3 2011

From our clinical colleagues:

"My heartfelt congratulations go out to Omar…. The entire BMT team is greatly pleased to be working with Omar." Robert K Stuart, MD

"Rob, you said it….thanks Omar for all of your fantastic work." Michelle Hudspeth M.D.

"Awesome! Well deserved. Congratulations!" Prabhakar K Baliga, MD

Dr. Omar Moussa receives qualification as Director of ASHI-accredited HLA laboratory

Inside this issue:

Janice Lage, M.D.,
Professor and Chair

FROM THE CHAIR

The American Society of Histocompatibility and Immunogenetics (ASHI) sponsors the American Board of Histocompatibility and Immunogenetics (ABHI). The ABHI provides four levels of certification including: Certified Histocompatibility Associate, Certified Histocompatibility Technologist, Certified Histocompatibility Specialist and a qualifying examination for Diplomate of the ABHI. In order to sit for this qualifying examination, a PhD candidate must complete a previously-approved educational program and pass rigorous written and oral examinations covering knowledge, experience and skills in histocompatibility and immunogenetics.

Omar Moussa, PhD, completed multiple years of research in immunology, a two-year Director's Training Program supervised by Drs. Howard Gebel and Robert Bray of Emory University and Dr. Rick Nolte of MUSC, passed the rigorous qualifying examination, and, lastly, passed a telephone interview evaluating his knowledge and problem solving abilities in additional areas of histocompatibility and immunogenetics. Now, having passed each hurdle, Dr. Moussa is qualified as a Director of the ASHI-accredited HLA laboratory at MUSC.

The ASHI confirmation letter further stated, "We appreciate the spirit with which you entered into the interview and manner in which you interacted with the referees. You are to be congratulated on your outstanding performance on the interview as well as your efforts in gaining the knowledge base and practical experience necessary to partner with our clinical and surgical colleagues in the fields of Histocompatibility and Immunogenetics." Well done, Omar!!

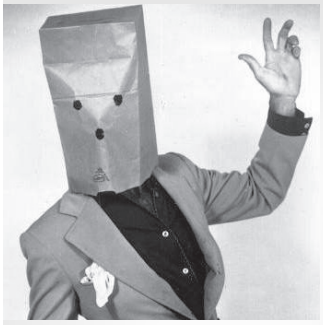
Mission Statement:
To serve patients, health care providers, research scientists, scholars, and society by providing excellence and innovation in diagnostic services and educational resources in a respectful, professional and culturally diverse atmosphere.

Vision:
To become a preeminent leader in academic anatomic and clinical pathology while translating basic science discovery to improved clinical care.

NEWS FROM DEPARTMENT ADMINISTRATION & BUSINESS OFFICE

Who's in the Spotlight?
IT COULD BE YOU

Please be sure to complete your nomination card.



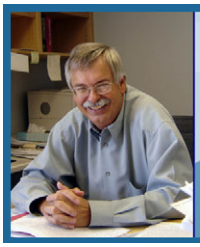
Nomination cards can be found at each of the Department's MUSC Excellence Communication Board locations: 2nd floor Walton Research Building and 3rd floor Children's Hospital.

Drawing will be held at the "All Hands Meeting" on October 19, 2011 in the 2W Amphitheater.

SERVICE AWARDS

Congratulations on reaching this milestone:

Sharon Ancrum	Venipuncture	**20 Yr.**
April Arrington	Molecular Pathology	10 Yr.
Gail Benton	Fast Flow	**20 Yr.**
Devonna Brown-Williams	Venipuncture (ART)	10 Yr.
Keisha Church	Molecular Pathology	10 Yr.
Weimin Fan, MD	Research	**20 Yr.**
Annette Hamilton	CytoPathology	**20 Yr**
Cindi Marchman	HLA Laboratory	10 Yr.
Emily Nowell	Venipuncture	10 Yr.
Martha Roddy	Cytopathology	10 Yr.
Devadoss Samuvel	Research	10 Yr.



Research Division Update

Bradley Schulte, Ph.D.
Vice Chair for Research

The Division of Research has had a productive time from April through June. Six grant proposals were submitted requesting $2,336,144 in total first year costs. Also, during this period eight grants were awarded totaling $1,849,316 over a one-year period (see table below). Congratulations and many thanks to everyone involved in obtaining these awards.

LaRue, Amanda	Fracture Repair by Mouse and Human Hematopoietic Stem Cells (VA Merit Grant)	4/1/11	**$150,000**
Sha, Su-Hau	Molecular Mechanisms in Noise-Induced Hearing Loss	4/1/11	**$355,933**
Moussa, Omar	The Role of Thromboxane A2 in Bladder Cancer A2 (TP) Receptor Beta in Bladder Cancer	4/1/11	**$296,881**
Mehrotra, Meenal	Hematopoietic Stem Cell Transplantation in Osteogenesis Imperfecta	4/1/11	**$69,027**
Singh, Avtar	Development of S-Nitrosothiol-based Therapy for Alzheimer's Disease (VA Merit Award)	4/1/11	**$150,000**
Singh, Avtar	Mechanisms of Krabbe Disease Pathobiology & Therapy	4/1/11	**$322,656**
Spyropoulos, D	Mammary Gland Laterality in Normal and Neoplastic Development (sub with USC)	4/1/11	**$182,163**
Singh, Avtar	Nitrosylation Mechanisms for Protection Against Neurovascular Inflammatory Injury	5/1/11	**$322,656**
TOTAL			**$1,849,316**

2011 STATE INSURANCE PROGRAM OPEN ENROLLMENT
OCTOBER 1 - OCTOBER 31

If your benefits are through the State Insurance Program, please note:

2011 Open Enrollment

Employees are encouraged to read the 2011 Insurance Advantage to learn about plan changes, premium increases and benefit updates for the 2012 plan year.

Employees will make changes to their insurance benefits through "My Benefits" , the website administered by the Employee Insurance Program, a division of the SC Budget and Control Board.

Open Enrollment is from October 1 - October 31, 2011.

All premium and plan changes are effective January 1, 2012.

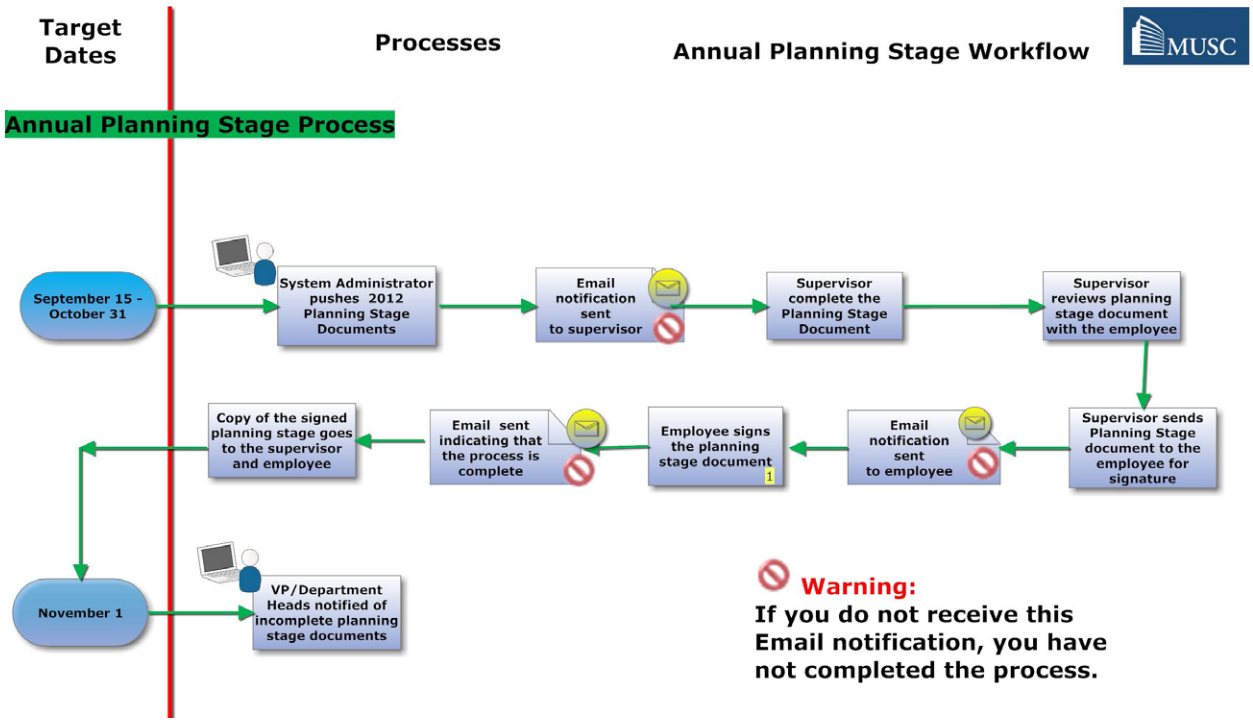
Insurance Advantage website

During Open Enrollment you may make the following changes:
-Change health insurance plan(i.e.: Standard to CIGNA)
-Add/drop health or dental for yourself or dependents
-Add/drop Dental Plus
-Add/drop the State Vision Plan
-Enroll/increase up to $50,000 of optional life insurance, in $10,000 increments, without medical evidence of good health*
-Decrease/cancel optional or dependent life insurance
-Enroll/re-enroll in Medical Spending or Dependent Care Accounts

University ------ Success Factors ----- Planning Stages

"Supervisors should have received email notification regarding planning stages that are ready to be completed"

A new online performance management system that automates the performance evaluation and goal management process and gets people more connected. It supports our organization's shift to a common review date.



IT Update by Tony Eisenhart

Password Management Made Easy

Passwords are absolutely essential in our digital lives. Unfortunately, our list of passwords, and the places we are required to use them continues to grow. It's not uncommon for a typical computer user to have 5 to 10 different passwords, often many more. So how are we supposed to create, manage, and remember all of them?

Start With a Good Strong Password

Perhaps the single most important thing to remember when creating a new password is make the password hard to guess, but easy to remember. That's easier said than done, but by following the guidelines below you will start using passwords that are more secure than what you're using now.

Passwords should always be at least 6-8 characters long. Passwords should never be a common word found in the dictionary. Passwords should always be free of any personal information such as your name, child's name, occupation, telephone number, address, or birth date. Your password should contain at least one letter and one numerical character and be a mix of upper-case and lower-case letters. Even stronger passwords should contain at least one punctuation mark or special character.

Techniques to Create Strong, but Easy-to-Remember Passwords

There are several techniques you can employ to make your existing passwords more robust. Whatever method you choose you should remember to make it an easy and understandable method so you will have stronger passwords without much more effort.

Acronym Method - Use the first letter from every word in your favorite expression, or line in a story, poem or movie. For example, "Badges? We don't need no stinking badges." could lead you to the following password: "B?wdNnSb".

Number Substitution - Choose a word as your password, but then substitute similar looking numbers for letters in your passwords. For example, Football may become "F00t8a77" or sneakers may become "5n3aK3r5". You don't need to associate every number with a letter. What is important is that you remember your list of associated letters and numbers.

Keystroke Technique - Choose a password that you want to use and then come up with a keystroke mapping system. For example, if you choose to do an "upper-left" keystroke mapping system you would choose the letter to the upper-left of the actual key you wanted. So if your password was "qwert" (not recommended) your new password would be "12345" (also not recommended). If the word you wanted to use for your password was football, your keystroke password would be "r995gqoo". It sounds complicated, but you need to look at your keyboard anyway, why not just choose the letter to the upper-left, left, or lower-right of the word you choose to remember.

Avoid Common Password Short Cuts

It's extremely difficult for people to remember several complicated passwords, passwords that we have to frequently change, or passwords we seldom use. As a result we all have a tendency to take shortcuts, shortcuts that should be avoided. Some write down their passwords on paper. Some store passwords in insecure files on their computer. Others might recycle and reuse combinations of the same passwords. You may rely on web browsers to remember their passwords. Or worst of all use simple easy to remember passwords that can be quickly and easily compromised. All of these shortcuts compromise security potentially exposing you, your family, or your employer to unnecessary risk.

We would like to welcome some new additions to the departmental staff:

Ashlyn Boserup – Lab Technologist II, August, 2011, will be working with Vinnie Della Speranza

Fu-Quan Chen – Visiting Scholar, July, 2011, will be working with Dr. Su-Hua Sha

Amy Gagliardi – Research Spec II, August 2011, will be working with Dr. Daynna Wolff

Lori Roten – Administrative Coordinator I, July, 2011, will be working with Dr. Janice Lage as assistant to the chair

Transferring from Graduate Studies to Pathology

Kayla Hill – Graduate Assistant, 2011, will be working with Dr. Su-Hua Sha

Jacqulyne Robichaux - Graduate Assistant, September, 2011, will be working with Dr. Demetri Spyropoulos

We bid farewell to:

Jonathan McGuirt – Research Specialist I, July, 2011, will be joining the cardiovascular perfusion program at MUSC

Paul Raptou – Lab Tech II, August 2011, will be furthering his career in the medical technologist program

New Faculty

Dr. Lee Marie Tormos

Forensic Pathology

Dr Tormos joined the faculty in Forensic Pathology in July. Dr. Tormos is a graduate of the University of Puerto Rico School of Medicine and is board certified in Anatomic and Clinical Pathology. Her professional interests include medical and forensic autopsy, organ and tissue donation for transplantation, blood banking, and quality assurance as it relates to the Medical and Forensic Autopsy Section.

Outside of work Dr. Tormos, says that her interest include her, "wonderful husband, two beautiful children, ages 10 and 1, two dogs and a cat. We enjoy traveling and home improvement projects and are in the process of looking for our next dream home improvement project!"

Dr. Anne Bartlett

Surgical Pathology

Dr. Bartlett is a native of Fort Wayne, IN. She received her undergraduate degree at Xavier University in Cincinnati before going on to medical school at Indiana University School of Medicine in Indianapolis. Dr. Bartlett is AP/CP certified and especially likes Surgical Pathology.

Her family includes her husband and two dogs. Outside of work, Anne says that her favorite activities are kayaking, walking her dogs and hanging out at the beach.

Dr. Dave Holloman

Surgical Pathology ENT Fellow

Dr. Holloman is a General Surgical/ Head and Neck pathology fellow this year at MUSC. Last year, he completed a Gastrointestinal and Liver pathology fellowship at the University of California, Los Angeles. Before his fellowships, he has been a resident at MUSC. According to Dave, "it is wonderful to be back! I am originally from Virginia Beach, Virginia and my wife (who also worked as a transcriptionist at MUSC, formerly Emily Calcutt) is from Lake City, SC. After my fellowship this year, we are hoping to stay somewhere in the southeast. I am hoping to work in general surgical pathology with some emphasis in gastrointestinal pathology."

Dr. Daniel Teague

Surgical Pathology

Dr. Teague received his M.D. degree here at the Medical University of South Carolina. He then performed his residency in Anatomic & Clinical Pathology at the Medical College of Georgia, in Augusta, GA. He returned to MUSC for a Surgical Pathology Fellowship. "I was born the second oldest of nine children in Canton, Ohio where I received most of my early education. Currently, my wife and I have four children, ages two to eight years. Outside of work I enjoy swimming, lifting, playing basketball and reading with my children, and coaching my son in baseball. Next year I plan to study dermatopathology at Wake Forest Medical Center."

Jane K. Upshur Post Sophomore Fellows

A Post-Sophomore Medical Student Pathology Fellowship Program

The Department of Pathology is pleased to announce the Pathology Post-Sophomore fellowship awards beginning the academic year 2010 in honor of an exemplary retired MUSC pathologist who has great dedication to pathology education. Each yearlong award (up to three) allows an interested and highly motivated medical student to pursue general and specialized pathology training within the department of pathology as well as design and/or participate in a research project within the department. Medical students may apply for the award from September 1 through February 15 of their sophomore or junior year for consideration for the following academic year. Two different concentrations are offered:

- **Clinical concentration:** 1 month (July) with the first year residents during their anatomic pathology introductory rotation, 4 months in surgical pathology, 2 months in medical and forensic autopsy, 1-2 months in hematology/ flow cytometry/cytogenetics/molecular pathology (1-2 weeks per service with an emphasis on hematological malignancy), and 3 – 4 months in electives, which may include or be comprised of a research project.
- **Research concentration:** 1 month (July) with the first year residents during their anatomic pathology introductory rotation, 4 months in surgical pathology, 1 month in medical and forensic autopsy, and 6 months in a clinical, basic science or translational research endeavor.

Students are awarded a stipend commensurate with current graduate school stipends, a $1,000 book fund and funding to attend a national pathology meeting. Additional funds are available for research support.

Please visit the pathology web site for details and information regarding application for these awards:
http://www.musc.edu/pathology/website/academics/medstudents/postsophomorefellow.html
or contact the program director: Cynthia A. Schandl, MD, PhD at schandlc@musc.edu.

J. K. Upshur Post Sophmore Fellows

Joanna Dalland

Joanna's current interest lies in forensic pathology. She believes that autopsies are an underutilized component of medicine, which has the ability to provide additional information to improve healthcare. "Pathology is one of the most important subjects taught in medical school, and the opturnity to further and apply this knowledge is an invaluable experience for any medical student."

Mia Taylor

"I would like to revisit organ systems, micro- and macroscopically and to acquire laboratory skills in an effort to facilitate my desires to participate in research during my career. I understand pathological processes to be the bases of the day to day practice of medicine, and a tremendous contributor to the shape of the human experience from occupational abilities, cultural attitudes and behavior."

Pathology Fellow

Natalie Mason, MD
Survey of Anatomic & Clinical Pathology

Natalie has done 2 years in general pediatric residency and is changing specialties in medicine. "I would like to spend this time in the field of pathology, learning and gaining skills that will help me in my career as a pathologist. I would also like the opturnity to gain some experience in the area of research."

New Fellows

W. Ashton Ennis, MD
Forensic Fellow

Ashton, who prefers to go by his middle name, was born in Alexandria, VA. He received his M.D. at Eastern Virginia Medical School, before going into a residency in Anatomic and Clinical Pathology at Allegheny General Hospital in Pittsburgh, PA.

He has a two year old son named Sam and lists his two hobbies as "Home brewing beer and drinkin' it."

Johann Hertel, MD
Cytopathology Fellow

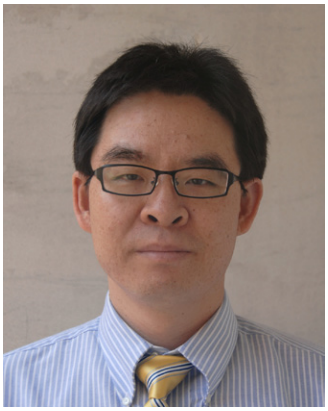
Johann was born at Lake Tomahawk WI. He received his M.D. at Washington University in St. Louis, Missouri before going on to a residency in Anatomic & Clinical Pathology at Barnes-Jewish Hospital in St. Louis, MO.

Shayna Tomchin, MD
Cytopathology Fellow

Shayna is a native of West Virginia, born in Bluefield. She completed medical school and did an Anatomic and Clinical Pathology residency at West Virginia University in Morgantown.

Todd Bruker, MD
Hemepath Fellow

Born Charles "Todd" Bruker in Decateur GA, Todd earned his M.D. at the Medical College of Georgia in Augusta. He completed a residency in Anatomic and Clinical Pathology at the University of Tennessee Medical Center in Knoxville, TN.



Zengliu Su, PhD
Special Chemistry Fellow

Zengliu (Leo) was born in the Peoples Republic of China. He received a PhD in Pathology at Iowa State University in Ames. Afterward, he completed a residency in Anatomic & Clinical Pathology at Vanderbilt University in Nashville, TN.

New Residents

Shannon Butler-Williams, MD

Born by the Pacific Ocean in San Francisco CA, Shannon attended St. George's University in the Caribbean and now joins us on the Atlantic Coast.

Lily Marsden, MD

A native of Salt Lake City, UT, Lily stayed close to home to attend medical school at the University of Utah. Now she has ventured east to Charleston.

Sherry Okun, MD

Sherry comes from a small town in the panhandle of Florida, named Niceville, and "yes," she says, "it's very nice there!" Sherry feels that the atmosphere of MUSC is right for her, and Charleston's deep Southern charm and hospitality, make her feel at home. Less thrilled at the move is Pico, her 12 year old, black and white, "miniature" greyhound who is extremely set in his ways. She believes she could build a career and home here … now if she can only convince Pico.

Tiffany O'Neill, DO

Tiffany says that she chose this program for the great location and friendly people. Professionally, she is interested in forensic pathology. Having lived in Florida for medical school, she wanted to stay in the southeast. Tiffany has two cats, Mia and Macy, that she considers her children. Formerly a competitive and synchronized swimmer, she swims as much as possible in her spare time.

Thomas Soike, MD

Born in Johnson City, TN, Thomas stayed there to attend medical school. As an East Tennessee State Buccaneer, he should feel right at home here in a city that has known its share of pirates and freebooters, provided we show him more hospitality than was given Stede Bonnet.

Kirtesh Patel, MD

A native of Greensboro in our sister state to the north, Kirtesh is another graduate of St. George's University in the sunny Caribbean. He nows joins our program in almost as sunny Charleston.

Sensory Hair Cell Survival and Death in the Inner Ear

By Su-Hua Sha, M.D., Assistant Professor

The cochlea is the sensory organ responsible for hearing and is involved in verbal communication. The sensory cells ("hair cells") of the organ of Corti are responsible for the transduction of acoustic input into nerve impulses, which are then transmitted to the brain. Damage to or loss of hair cells leads to permanent hearing loss, as mammalian hair cells lack the ability to regenerate. According to the Center for Hearing and Communication, an estimated 38 million people in the United States – one of every ten Americans – have hearing loss, which imposes a huge detriment to the quality of life of the affected individuals and a formidable economic challenge on society.

Hearing loss can be divided into two general categories: genetic and acquired. Our research focuses on acquired hearing loss, which is hearing loss that develops during one's lifetime secondary to exposure to influences noxious to the inner ear. Exposure to excessive noise or ototoxic drugs (e.g. aminoglycoside antibiotics and the anti-cancer agent cisplatin), and aging are the three main causes of acquired hearing loss. The histopathological hallmark of acquired hearing loss is the destruction of the hair cells in the inner ear, leading to a permanent loss of hearing.

Our laboratory is investigating the redox-regulated signal transduction pathways of acquired hearing loss, primarily of noise-induced hearing loss. Our primary goal is to elucidate the molecular mechanisms that determine the fate of inner ear sensory cells, dictated by whether the pathways leading to cell death or to cell repair and survival prevail. A further goal is to translate our research findings into clinical therapies to prevent or ameliorate the adverse effects of acquired hearing loss.

Personnel in the Sha laboratory:
Carlene Brandon: Research Specialist (II)
Kayla Hill: Graduate Student
Fu-Quan Chen: Post-doc Research Fellow
Hong-Wei Zheng: Post-doc Research Fellow
Alison Kearns: Summer Research Student

Noise-induced hearing loss (NIHL)

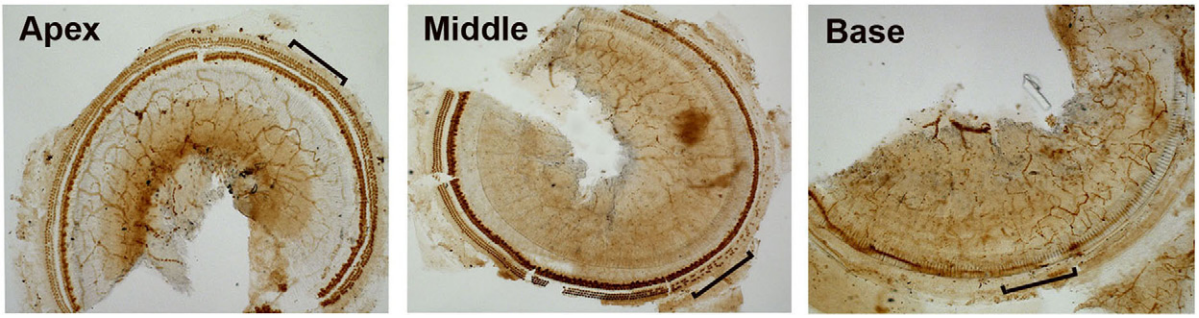
It may be surprising that the auditory system, designed to process acoustic information, is sensitive to and can be damaged by intense sound. Today, NIHL is a major problem and is increasing in industrialized countries, stemming both from the workplace and from leisure activities. While most of the public is aware of the dangers of industrial and machinery noises, gun shots, and airplanes, many seem to disregard the dangers they impose upon their hearing at music concerts and with headphones at high volumes. Tinnitus (ringing in the ears), temporary hearing loss, and permanent hearing loss all are possible consequences of these exposures.

Research into NIHL using animal models has borne out two leading theories for the cause of hearing loss. One is mechanical damage from vibration of the organ of Corti beyond the tolerance of its physical structure. Another is a so-called 'metabolic damage', wherein metabolic overstimulation and stress trigger cell death pathways. A variety of biochemical and molecular responses in response to noise trauma have been identified. For example, noise exposure elevates intracellular calcium levels in hair cells, probably through influx via calcium channels, and also activates calcineurin, a calcium-dependent phosphatase. Another well-documented response to noise trauma is the generation of reactive oxygen species (ROS). It appears that excessive noise decreases cochlear blood flow, which causes vasoactive lipid peroxidation and leads to generation of ROS. In addition, release of the neurotransmitter glutamate at inner hair cell synapses in response to traumatic noise has been implied in excitotoxicity (neuronal damage and cell death from overstimulation by neurotransmitters) at this synapse.

Traditional prevention of NIHL by use of ear plugs to reduce noise levels reaching the ear has proven insufficient, primarily due to non-compliance. Based on animal experimentation, pharmacological prevention, using a

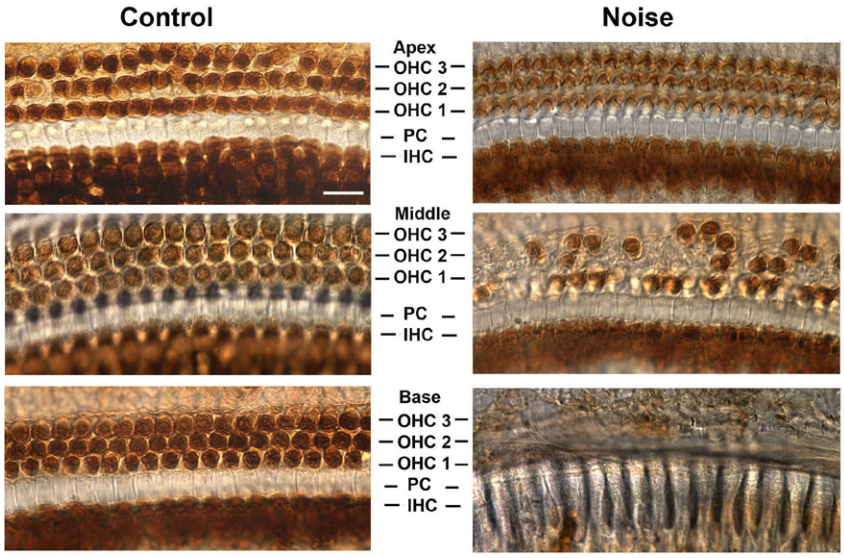
Left to right
Back row: Hong-Wei Zheng, Tiffany Baker, Fu-Quan Chen
Front row: Su-Hua Sha, Carlene Brandon, Alison Kearns, Kayla Hill

"hearing pill", is currently a promising route. Antioxidants such as glutathione, D-methionine, ascorbic acid, and water soluble coenzyme Q10 have been reported to attenuate NIHL to some extent, while other antioxidants have failed to prevent NIHL. These conflicting results underscore the challenge still faced by the field in elucidating detailed molecular mechanisms and preventing NIHL.



Above images were taken with a 10X lens along the entire length of mouse cochlear surface preparations 2 weeks after exposure to 106 dB SPL 2-20 kHz broadband noise. No hair cells were missing in the apical region, while both outer and inner hair cells were completely destroyed in the basal region. An interesting pattern was observed in the middle segment of the cochlea. Hair cells were intact in the portion of the middle region nearest to the apex, while in the portion nearest to the base, outer hair cell loss ranged from partial to complete, although inner hair cells were still present.

The images to the right were taken with a 63X lens. Control mice illustrate the normal structure of the sensory epithelium with three rows of outer hair cells (OHC), one row of inner hair cells (IHC) and pillar cells (PC) from the apical, middle, and basal regions of the mouse cochlea. Noise exposed mice showed complete hair cell loss in the basal turn, partial hair cell loss in the middle turn, and no hair cell loss in the apex of the mouse cochlear epithelium. Scale bar = 10 µm.



Aminoglycosides and age-related hearing loss

Interestingly, noise- and aminoglycoside-induced hearing loss and age-related hearing loss share similar inner ear pathologies, and, at the very least, share oxidative stress as a pathological feature. We are, therefore, extending our studies to drug-induced and age-related hearing loss in collaboration with Dr. Jochen Schacht at the Kresge Hearing Research Institute at the University of Michigan. Both in-vivo and in-vitro studies from our laboratories have convincingly shown that oxidative stress is a causative factor in aminoglycoside-induced hearing loss and that this ototoxicity can be attenuated by the administration of antioxidants. We have collaborated with colleagues in the Department of Otolaryngology at Xijing Hospital in Xi'an, China, on a clinical study to protect against gentamicin-induced hearing loss using aspirin. Successful results showing a 75% reduction in the incidence of hearing loss were published in the New England Journal of Medicine in 2006. To date, this study shows the most striking protection reported against aminoglycoside-induced hearing loss and illustrates the principle that acquired hearing loss can be prevented with pharmacological interventions.

We have also collaborated in a program project grant studying the mechanism of age-related hearing loss (presbycusis) with other groups at the Kresge Hearing Research Institute and the Geriatrics Center at the University of Michigan. Our studies involve the assessment of free radical formation and cochlear antioxidant defenses as well as redox-sensitive homeostatic signaling pathways that engage protein kinases and phosphatases.

Investigation of redox signaling and cell death pathways in all three pathologies is a part of our ongoing effort to understand hair cell death and, ultimately, its clinical prevention.

Current Funding
PI Sha: NIH/NIDCD R01 DC 009222 "Molecular Mechanisms in Noise-induced Hearing Loss"
PI Sha: Sub-Award No 3001616970, NIH/NIDCD R01 DC003685 "Protection from Aminoglycoside Ototoxicity"
Pending Funding
PI Sha: RNID Translational Research Initiative for Hearing (TRIH) "Protection against noise- and aminoglycoside-induced permanent hearing loss"

Molecular Oncology Testing At MUSC

Julie Woolworth, Ph.D. Associate Director of Molecular Pathology; Rick Nolte, Ph.D. Director of Molecular Pathology and Clinical Laboratories; Daynna Wolff, Ph.D. Director of Cytogenetics

At present, the largest segment of the molecular diagnostics market is infectious disease, however, this could change within a few years giving way to molecular oncology testing. Currently, the molecular oncology market is the second largest segment in molecular diagnostics market and the development of new assays surpasses that of infectious disease. The largest contributor to the increase in the development of new molecular oncology assays is an increased understanding of molecular mechanisms promoting cancer progression combined with the development of new therapies against these molecular targets. Molecular targets in cancer can have a wide range of utilities including diagnosis, prognosis, disease monitoring and assessment of therapeutic response. Molecular diagnostic testing can be static, only tested once, or dynamic, the target is tested often during and after treatment.

Testing Currently Offered:

- EML4-ALK by FISH
- HER2 by FISH
- UroVysion™ by FISH
- HPV testing
- EGFR mutation analysis
- KRAS mutation analysis
- BRAF V600E mutation analysis

Future Molecular Oncology Testing:

- BCR-ABL Quantitation
- B and T cell clonality
- Chimerism Testing
- Microsatellite Instability
- HPV 16/18 Genotyping

Currently at MUSC, we offer a battery of fluorescence in situ hybridization (FISH) assays utilizing single probes or panels of probes for a wide variety of leukemias and lymphomas. In addition, FISH for HER2 is currently being used to aid clinicians in determination of the appropriate therapy for breast cancer patients and UroVysion FISH is used to diagnose and monitor patients for bladder cancer. For other solid tumors, we have been busy in the clinical laboratories building up a menu of diagnostic assays for a variety of tumor types including lung and colon cancers and melanoma. The process of molecular oncology testing relies on effective communication and interpretation between the clinicians, pathologists, and laboratory staff. One concern with molecular oncology testing is the development of guidelines for the right test to be used on the right patient. To address these concerns, most of our testing algorithms are taken from the National Comprehensive Cancer Network (NCCN). The NCCN is a collaboration between 21 of the most well-known cancer centers across the United States that compile clinical practice guidelines for use by patients, laboratories, and physicians. The group develops cancer-type specific guidelines based on evidence-based consensus-driven data. In addition to the NCCN guidelines, in-house testing allows for a dialog between the molecular pathology laboratory and the physicians regarding testing that should be done here at MUSC.

Since January of this year, the Molecular Pathology Laboratory has been working hard to bring in-house, each member of the NCCN current testing algorithm for non-small cell lung carcinoma (NSCLC). NSCLC accounts for about 85% of lung cancer diagnosed each year. There are three main types of NSCLC: squamous cell carcinoma (25-30%), adenocarcinoma (40%), and large-cell (undifferentiated) carcinoma (10-15%). Lung cancer accounts for approximately 14% of all cancer that will be diagnosed this year. Lung cancer is responsible for more deaths due to cancer in men (28%) and women (26%) than any other cancer. Treatment options for lung cancer are first determined by the type of cancer – small cell or non-small cell. Other considerations for treatment options include stage of the cancer. Treatment options include surgery (mostly for localized cancers), radiation therapy, chemotherapy, and targeted therapies. Advanced stage diseases often see the greatest benefit from the use of targeted therapies in combination with chemotherapy. Two tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR) drugs have been FDA approved for the treatment of metastatic NSCLC: gefitinib (Iressa) and erlotinib (Tarceva) [1-3]. Recommendations for these medications include testing for EGFR and KRAS mutations. The presence of certain EGFR mutations, including deletions in exon 19, a single nucleotide polymorphism, SNP, in exon 21 (L858R), and three SNPs in exon 18 (G719A, G719S, G719C) have all been associated with an increased response to the TKIs. The presence of other mutations in the EGFR gene have been associated with a lack of response to TKIs, these mutations include T790M, S796I, and nucleotide insertions in exon 20. The EGFR receptor is involved in the cell growth signaling pathway and the presence of these mutations can cause activation of the EGFR receptor leading to uncontrolled cell division in the lung cancer cells. The EGFR mutations shown to respond to TKI therapy all activate the receptor in the tyrosine kinase domain and therefore preferentially bind to the drug, as opposed to normal ligand, and the cancer cells then stop signaling and eventually die. The presence of EGFR mutations in NSCLC is around 10% and the majority of these mutations are deletions in exon 19 and L858R. Our laboratory uses allele-specific RT-PCR to identify the mutation status of EGFR looking for 29 different known EGFR mutations. Downstream from EGFR signaling is KRAS.

Mutations in the KRAS gene in NSCLC have been shown to cause constitutive activation of the KRAS protein and cell proliferation. So, if a KRAS mutation is present in the metastatic tissue, then likely the patient will not respond to the anti-EGFR TKI therapy. KRAS mutations are present in 40-60% of patients with metastatic NSCLC. We currently use allele-specific RT-PCR to

identify 7 KRAS mutations in codon 12, 1 mutation in codon 13, and 4 mutations in codon 61.

A third molecular diagnostic recommended for NSCLC testing is a rearrangement between the anaplastic lymphoma kinase (ALK) and echinoderm microtubule-associated protein-like 4 (EML4). EML4-ALK rearrangements are observed in about 9-10% of NSCLC and the presence of a rearrangement is associated with increased response to ALK inhibitor therapy. ALK rearrangement is determined by fluorescence in situ hybridization (FISH) analysis.

NCCN guidelines recommend the same KRAS mutations be analyzed to determine if metastatic colorectal cancer patients will respond to anti-EGFR therapy. Colon cancer is the third most common cancer in men and women in the United States. Surgery is a favored option to remove the tumor or resection of part of the cancerous colon. It is recommended that all patients with Stage III or greater colon cancer should receive chemotherapy after surgery. It has been found that the monoclonal antibodies directed against EGFR, cetuximab (Erbitux) and panitumumab (Vectibix) are more likely to clinically benefit patients with metastatic tumors that express endogenous EGFR and wild type KRAS. About 60% of patients express wild type KRAS, while the remaining 40% have an activating mutation causing the patients to not respond well to therapy [4, 5]. In addition, an activating mutation, V600E, in the BRAF gene, that is also downstream in the signaling pathway from EGFR, is associated with a poor prognosis compared to patients with wild type BRAF expression. Retrospective studies have shown that the presence of a BRAF V600E mutation is a marker of lower response rate to the EGFR monoclonal antibodies once they have failed first-line therapies. To test for KRAS, we use the same allele-specific RT-PCR used to identify the mutation in NSCLC and an allele-specific RT-PCR test to identify the V600E mutation status of the BRAF gene.

Testing for BRAF V600E mutation status is also valuable in patients with metastatic melanoma. The introduction of the first BRAF inhibitor, vemurafenib (Zelboraf), to the drug market has provided a new effective treatment for patients with metastatic melanoma that harbor the V600E mutation. In the recently published phase 3 clinical trial, vemurafenib was shown to improve progression-free survival, although survival past 6 months has not been released yet because the data is not mature enough [6]. Again, we use an allele-specific RT-PCR assay to identify the presence of a V600E mutation. Since the introduction of the BRAF inhibitor there have been a handful of publications to suggest that other mutations in the BRAF gene, in particular V600K, should be tested for response to BRAF inhibitor therapy [7, 8]. We will continue to be vigilant and stay well-informed of all new evidence for testing and will be prepared to offer the testing of any other relevant mutations as soon as they are shown to clinically beneficial.

The field of molecular oncology testing is a great example of the personalized medicine concept. The ability to use targeted therapies to tailor a patient's therapies is making medicine individualized and the outcome is better patient care and disease management. Here at MUSC we have a vision for our clinical testing that expands our local molecular oncology testing menu to include the quantification of the BCR-ABL1 fusion gene, B and T cell clonality, chimerism testing for bone marrow transplant monitoring, microsatellite instability, and HPV 16/18 genotyping. We have already begun to see a great benefit from doing molecular oncology testing here at MUSC. First, we have become better stewards of our patient's tissue. The laboratory is able to work closely with our pathologists to determine the best sample of tissue to take for the assays and the best way to conserve remaining tissue for any future testing that might be necessary. Our pathologists have been such a valuable asset to bring this testing to MUSC and are necessary for its success. Second, we are able to have greater control over the test turn-around time. The clinicians are able to get the results almost instantaneously once the testing is performed.

For EGFR, KRAS, and BRAF:
DNA is extracted from samples on Tuesdays at 10am and assays run on Wednesdays.

FISH testing for HER2 and EML4-ALK is done M-F, as needed.

Third is the potential for increased clinician satisfaction because they have the ability to interact with the people performing the test in real time. Overall, increasing the molecular oncology test menu offered at MUSC has the potential to increase both patient and physician satisfaction and we are happy to be of service in support of the Hollings Cancer Center clinical enterprise.

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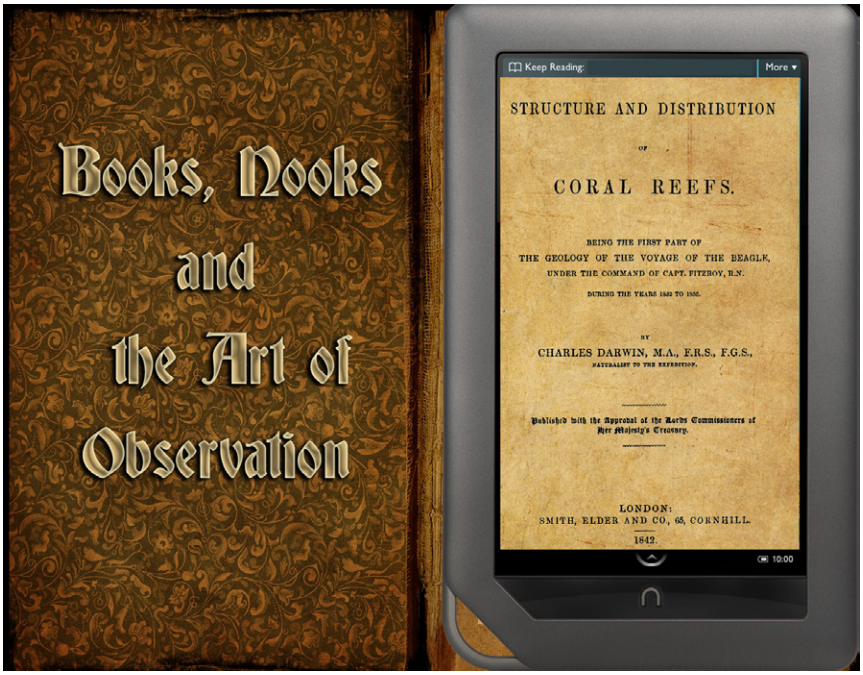

By James H. Nicholson

I confess to being an incurable and thoroughly unrepentant bibliophile. It's a hereditary affliction since I acquired it while accompanying my father on weekend expeditions to repositories of long forgotten tomes. My personal favorite was Laudermilk's, where dusty books filled crowded bookcases on six floors of an old mill building beside the Chesapeake & Ohio Canal in the Georgetown section of Washington D.C. This acorn didn't fall far from that tree, except I can shop thousands of little bookstores without leaving my desk chair. Dad spent years trying to collect the complete works of a little known 19th century author, John Esten Cooke. Today, by merely clicking on Abe Books.com I can choose from almost 3,000 copies. That's dangerously convenient for a confirmed book worm.

Fortunately, just as my disposable income, available floor space and wife's patience were all exhausted, technology came to the rescue. Thanks to my Color Nook (Sorry Kindle, but I've got to see those color plates) I can carry an entire library in a slightly oversized pocket. I especially like the old classic books of science and history and almost all of them are free from sources like Google Books. Google estimates that there are 129,864,880 unique books in the world, and they plan to scan them all by the end of the decade.

Heresy you say; no electronic gadget can ever give the tactile pleasure of a beautifully bound book. Probably not, although it is possible to get a nice leather cover for your gizmo. However, it's a moot point because I could never hope to own most of these books. For example, last night I was reading the 1842 first edition of "The Structure and Distribution of Coral Reefs," by Charles Darwin. If you want that particular tactile pleasure, there is a copy available for $15,000.

Which is my clever segue to the real topic of my little treatise; namely that reading old books of science shows how truly remarkable discoveries were made using the eyes and the brain – observation and reasoning.

When Darwin set sail in the *Beagle* in 1831, the origins of isolated coral atolls was considered a major scientific mystery. The leading London literary journal considered the investigation of this phenomenon the most important mission of the expedition.

Sailing ships of the day provided nothing if not time to think, and Darwin had reasoned out the probable answer before he actually set eyes on a coral reef. At first opportunity he dove on some actual reefs and confirmed his supposition that the rings of coral were once fringing reefs around an island that had since subsided into the ocean. Since the sinking of the island was slow, the coral was able to maintain a hospitable depth through normal growth. Eventually the reef circled the location of what had once been land but was now deep ocean. It was a long leap since there was no mechanism known that could account for the subsidence of land masses. It was too big a leap for many of his contemporaries and the often bitter debate was not finally laid to rest until the 1950s when deep core drilling finally proved his concept once and for all. It had taken almost 120 years to develop a technological tool to confirm what Darwin had discovered by observation and reasoning.

Advancing science by actual physical observation seems obvious now, perhaps even a bit quaint, but in 1831 it was a revolutionary concept that was gradually replacing the classic philosophical approach which called for reading, not doing.

Medicine was in the forefront of this revolution. The science of medicine relied on observation and insight having few other tools available to gather information. Many physicians were renowned for their observational skill, but few more than Dr. Joseph Bell, a 19th century lecturer at the medical school of the University of Edinburgh. Bell is considered a pioneer in Forensic Pathology before the discipline was known by that name, or much used in criminal investigation.

Joseph Bell amazed his students with his ability to know the occupation and background of a patient by observing their mannerisms, stride, musculature, callouses and other fine details. A young Conan Doyle was his student and later served as his ward assistant. It is generally conceded that Bell inspired and served as a model for Doyle's immortal fictional detective, Sherlock Holmes. Bell, however, did not perform these feats merely to entertain his students.

"*In teaching the treatment of disease and accident, all careful teachers have first to show the student how to recognize accurately the case. The recognition depends in great measure on the accurate and rapid appreciation of small points in which the diseased differs from the healthy state. In fact, the student must be taught to observe. To interest him in this kind of work we teachers find it useful to show the student how much a trained use of the observation can discover in ordinary matters such as the previous history, nationality and occupation of a patient*." Dr. Joseph Bell.

The audio-visual side of my career is responsible for my attendance at a great many Clinical Pathological Conferences, first at Duke University and later here at MUSC. One thing that I personally learned from these sessions was that in a majority of the cases the patient was first placed on the slippery slope to a disastrous outcome by an oversight or misinterpretation made in gathering the history and performing the physical diagnosis at the primary level. Regrettably, the constraints and realities of modern medical practice tend to diminish the time a physician can spend with a patient and make complete and accurate observation all the more difficult.

Observation alone however is useless unless there is time and ability to recognize the significance of that which is observed. In 1881, Fannie Hesse, who was working as a technician for Robert Koch, suggested using agar to set up nutrients in a petri dish, an idea she got from making jam. Scientists now had an effective method to culture bacteria, and almost immediately began noticing how certain mold "contaminants" tended to inhibit growth or even kill the bacteria. This was regarded and treated primarily as a nuisance.

Andre Gratia and Sarah Darth presented a paper in the 1920s describing in detail how a species of Penicillium inhibited the growth of *Staphylococcus aureus* cultures. Nobody paid any particular attention. Possibly they were all too busy looking for a "magic bullet" with which to fight bacterial disease.

In 1928, the nickel dropped for Alexander Fleming and he grew a pure culture of *Penicillium notatum* and isolated the active component penicillin…and spent a dozen years trying to rouse enough interest in any chemist that might be willing to help him develop and stabilize his discovery. Without the impetus of a World War he might not have gotten support even then.

There is a story that Albert Einstein was walking across the campus at Princeton, his mind no doubt busy wrestling with the elusive unified field concept. He walked into an overhanging tree branch and was knocked to the sidewalk stunned. A concerned bystander rushed to his aid and asked him if he hadn't seen the offending limb. Einstein reportedly replied, "I saw it, I just didn't comprehend it."

There is a justified concern that under pressure to write grants and publish papers, our most talented scientists may gather more and more data, with less and less time available to comprehend its meaning.

Perhaps there is something to be said for slow moving sailing ships. The voyage of the *Beagle* was planned originally to last two years but ended up lasting almost five. From that trip, Darwin solved the puzzle of coral atolls, gathered the essential clues that lead to his theory of evolution and recorded important observations in the fields of geology and anthropology. He published his findings in four thick volumes which were immediate "best sellers" and were reprinted in numerous editions. How many modern scientists can hope to look back on a five year period of their career with the feeling that they have accomplished as much.

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Pathology Spring Symposia

Speakers Announced for 2012 Symposia

The faculty is being assembled for the Pathology Spring Symposia to be held at Kiawah Golf Resort, April 23-28, 2012. The focus will be on the role of molecular testing in the diagnosis and treatment of malignancies.

Pratt-Thomas Symposium in Surgical Pathology

Samuel A Yousem, MD
University of Pittsburgh, Pittsburgh, PA

Marisa Nucci, MD
Harvard Medical School, Brigham and Women's Hospital, Boston, MA

Anthony Montag, MD
The University of Chicago, Chicago, IL

Edward F McCarthy, MD
Johns Hopkins University, Baltimore, MD

David Lewin, MD
Medical University of South Carolina, Charleston, SC

John R Goldblum, MD
Cleveland Clinic, Cleveland, OH

Wade Samowitz, MD
University of Utah, ARUP Laboratories, Salt Lake City, UT

Peter A Humphrey, MD, PhD
Washington University, St. Louis, MO

McKee Cytology Seminar

Michael R Henry, MD
Mayo Clinic, Rochester, MN

Martha B Pittman, MD
Harvard Medical School, Massachusetts General Hospital, Boston, MA

Richard M DeMay, MD
The University of Chicago, Chicago, IL

Gadsden-Holbrook Symposium in Clinical Pathology

Gerard A Silvestri, MD, MS
Medical University of South Carolina, Charleston, SC

Frederick S Nolte, PhD
Medical University of South Carolina, Charleston, SC

Daynna J Wolff, PhD
Medical University of South Carolina, Charleston, SC

Elaine Mardis, PhD
Washington University, St. Louis, MO

Adam Bagg, MD
The University of Pennsylvania, Philadelphia, PA

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