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Pathology and Laboratory Medicine Newsletter

Letter from the Chair

MUSC Pathology and Laboratory Medicine is poised to be in the top quartile of American Medical Schools in the next decade.

Look how we have grown in our Department alone:

RESEARCH:

- Our national **NIH funding rank** went from 84th to 44th for US academic medical schools (\$394,000 in 1999 to over \$4.4 million 2009)
- Establishing a **Urologic Cancer Research Center** in the Walton Research Building in collaboration with Dr. Andrew Kraft, Director, Hollings Cancer Center and Dr. Thomas Keane, Chairman, Urology
- NIH funded laboratory renovations in **Age-Related Hearing Loss** program project research

SERVICE:

- One of the largest **Point-of-Care Testing** laboratory programs in the US
- Leaders in **Patient Safety** with new molecular laboratory tests identifying infectious bacteria more accurately and more quickly, measuring viral loads, and establishing a **Global Initiative for Patient Safety Excellence**
- New **innovative instrumentation** in the clinical laboratory for immunosuppressant drug level analysis, improving transplant patient care by faster test result reporting
- Leadership roles in all three major **academic and private practice Pathology societies** in the US
- **Outreach facilities** at Oconee Medical Center with telepathology capabilities, East Cooper and the North Area

EDUCATION:

- Leadership role in developing MUSC's **New Curriculum** for medical students and a new Pathology Course for dental students
- Leaders in **Pathology Residency Training Programs** in the Southeastern US; developed new **Fellowship Training Programs** in Histocompatibility (HLA) and Clinical Chemistry
- Established **Gordon R. Hennigar, Jr., M.D. Endowed Chair in Pathology**
- Substantial funding of the **H. Rawling Pratt-Thomas, M.D. Endowed Chair in Pathology**



Coagulation Laboratory's Role in the Diagnosis and Management of Patients with Thrombotic Disorders



By: John Lazarchick, M.D., Director, Hematopathology

The primary cause of morbidity and mortality in the US population is due to thrombotic disease, both arterial and venous. Platelets play a central role in initiating and perpetuating the thrombotic process. The pharmaceutical industry has focused a great deal of its research effort in developing anti-platelet agents to inhibit specific areas of platelet function including those related to adhesion, activation with release of cytoplasmic granule content and aggregation. Our laboratory has been able to monitor the efficacy of these drugs using classical platelet aggregation/ATP release with the Chrono-Log analyzer. This method, however, is labor intensive, time-consuming and costly. We now have in place a Point-of-Care instrument from Accumetrics, the Verify Now analyzer assay system to specifically monitor the inhibition of platelet ADP receptor P2Y₁₂ in patients being treated with thienopyridines, clopidogrel (Plavix) or prasugrel (Eflent) in addition to cyclooxygenase inhibitors including aspirin (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs). Plavix and ASA are given to all patients undergoing coronary stent procedures. Approximately 30% of patients receiving clopidogrel, however, have no evidence of ADP receptor inhibition (Plavix-resistant). Plavix is a pro-drug that requires activation by cytochrome P450 isoenzymes before it can inhibit platelet function. Polymorphism in the hepatic enzymes involved may explain this resistance. Eflent is a direct inhibitor of the ADP P2Y₁₂ receptor and does not require an intermediate step. To further evaluate the most effective therapy in the Plavix-resistant group, our laboratory will be participating in a collaborative study with the interventional cardiologist group in identifying this group of patients prior to their undergoing a stent procedure. This will involve screening patients referred to the Cardiology Division with the Verify Now assay system to demonstrate lack of inhibition and then molecularly immunophenotyping the CYP2C19 alleles of this subset of patients. It is projected that the study will involve approximately 100 patients with one study group receiving increasing doses of clopidogrel and the second group receiving prasugrel which is not metabolized by the CYP2C19 system. All patients will be monitored with the Verify Now assay for extent of platelet inhibition and clinically assessed for the efficacy of therapy and risk of bleeding.

A second study sponsored by Helena Laboratories is being done in collaboration with Dr. David Steinberg of the Interventional Cardiology group. Patients undergoing coronary stent placement are anticoagulated during the procedure. This is typically done using unfractionated heparin and the level of anticoagu-

lation is monitored by performing an Activated clotting Time (ACT) using the iSTAT point-of-care instrument. Excess bleeding secondary to heparin is a complication that has an adverse effect on outcome. Our study is part of a multi-institutional effort to assess the safety and efficacy of the use of bivalirudin, a direct thrombin inhibitor, to achieve anticoagulation. Bivalirudin has a lower incidence of intra-operative bleeding and theoretically would be the superior mode of anticoagulation. The anticoagulant effect will be monitored using Helena Laboratories point-of care instrument, the Abrazo Analyzer, and their DTI assay card. Samples will be drawn before the drug is given, 5 minutes after infusion and at the end of the procedure. Clotting times from this system will be compared to the ACT determination performed on the iSTAT analyzer.

“Critical role of the coagulation laboratory in the diagnosis and therapy of hypercoagulable Disorders”

Stent procedure outcomes related to stent thrombosis, excess bleeding and survival will be assessed by the Interventional Cardiology group.

The other area of major change involves the laboratory's diagnostic assays for confirming hypercoagulable states (Thrombosis Panel). These include functional coagulation assays (PT, aPTT, AT-3, protein C, free protein S, StaClot for lupus anticoagulant), ELISA assays (APA IgG and IgM titers to aCL, phosphatidylserine and phosphatidylinositol, the latter being cell surface phospholipids involved in the coagulation process) and molecular assays (Factor V Leiden and prothrombin mutation). We will now incorporate the Dilute Russel Viper VenomTime (DRVVT) as a second assay for the detection of lupus anticoagulants and testing for the APA syndrome will include IgG and IgM APA titers to beta 2 glycoprotein 1. There is sufficient clinical evidence now which would suggest that the presence of a lupus anticoagulant or APA antibodies to beta 2 GPI have the highest risk of developing a thrombotic event, either arterial or venous, increased risk of pregnancy loss or isolated thrombocytopenia. These additions should allow our clinicians a state-of-the-art comprehensive evaluation profile for the evaluation of suspected hypercoagulable disorders.

Stem Cell Group

By: Makio Ogawa, M.D., Ph.D.
Professor, Pathology and Laboratory Medicine



Left to Right: Makio Ogawa, MD, PhD, Haiqun Zeng (HCC), Christopher Williams, Meenal Mehrotra, PhD, Amanda C. LaRue, PhD, Lindsay T. McDonald, and Karen Rivers. George Washington not pictured.

Members

Makio Ogawa, M.D., Ph.D. joined MUSC and the VA in 1973 and began studies of the cellular physiology of hematopoietic stem cells (HSCs), blood cell-producing stem cells. In 2000, Dr. Ogawa began to focus on stem cell plasticity. In order to clarify the controversies surrounding the subject, he developed an efficient method for single HSC transplantation and began systematic studies of the tissue reconstituting abilities of HSCs. As a necessary technology for these studies, he also brought FACS cell sorting and analysis to MUSC and ran a campus-wide service until 2008.

Amanda LaRue, Ph.D. joined the group in 2003 as a Postdoctoral Fellow after receiving research training in cell and developmental biology at MUSC. After completion of her fellowship, Dr. LaRue was appointed as an Assistant Professor and Research Health Scientist with the VAMC (2005). Dr. LaRue has collaborated in the studies of tissue reconstituting capabilities of HSCs with specific focus on the identification and functional characterization of HSC-derived cells both *in vitro* and *in vivo* using cell culture, animal injury models, immunohistochemistry, microscopy and imaging.

Meenal Mehrotra M.D., Ph.D. was recruited in 2007 to participate in this group based on her expertise in bone and mineral metabolism. She obtained a Ph.D. in Endocrinology in 2003 (Lucknow, India) and completed a Postdoctoral Fellowship investigating signal transduction pathways involved in mechanical loading and bone remodeling (2006, University of Connecticut Health Center).

Karen Rivers has assisted the administration since 1996, facilitating the group's interaction between MUSC and the VA. **Christopher Williams** has assisted the group as a Research Specialist since 2008. He was recently accepted to MUSC for the fall 2010 Medical School class. **Lindsay McDonald** is a first year PhD graduate student working with Dr. LaRue. **George Washington** has been with the group since 1995.



Shirai et al, 2009, Cover Image

Collaborators

Pathology and Laboratory Medicine: Dennis K. Watson, PhD, Omar Moussa, PhD, Bradley A. Schulte, PhD, Hainan Lang, PhD, John Lazarchick, MD; Medicine: Patricia M. Watson, PhD, Keisuke Shirai, MD, Robert Stuart, MD; HCC: Haiqun Zeng.

Research

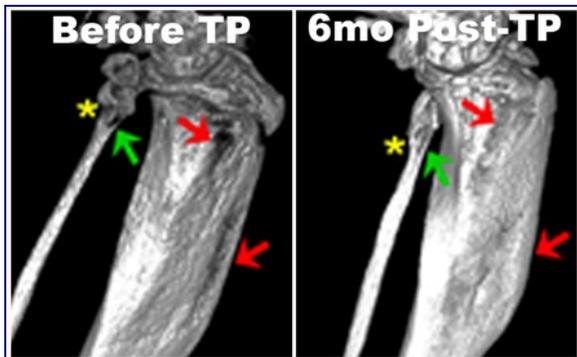
The group's primary research focus is the pathophysiology of HSCs. Using the single cell transplantation model developed by Dr. Ogawa, this group is investigating the tissue reconstituting ability of HSCs in both normal and pathological models. Their early findings demonstrated that HSCs give rise to fibroblasts/myofibroblasts in a number of tissues and organs including brain, heart, liver, and kidney. Transplantation studies have also shown that HSC-derived carcinoma-associated fibroblasts (CAFs) promote tumor progression, suggesting a novel target for anti-tumor therapies.



Sera et al., 2009, Cover Image

More recently, these investigators have generated strong evidence that all adult connective tissues, including loose and dense connective tissues, fat tissues, bone and cartilage, are produced by HSCs.

Stem Cell Group Cont.



HSC transplantation for Osteogenesis Imperfecta.

This concept has an immediate impact on the treatment of injuries to and genetic diseases of the connective tissues. For example, modulation of HSC participation in fracture repair may provide a therapy for non-union. In addition to osteogenesis imperfecta (OI), such genetic diseases as epidermolysis bullosa, Alport syndrome and leptin deficiency should be treatable with HSC transplantation. There has been significant interest in the use of stem cells for therapeutic purposes as illustrated by several ongoing clinical trials based on mesenchymal stem cells (MSCs), but these trials have been hampered by low engraftment rate and the heterogeneity of the MSC population. Studies from this group suggest that HSCs provide a readily available population of adult stem cells for sustained engraftment and a long-term therapeutic source of connective tissue cells.



Dr. LaRue, Dr. Ogawa, Chris Williams and Lindsay McDonald.

Facilities

The laboratory of the group is located on the 4th floor of the Strom Thurmond Biomedical Research Building. This lab houses HCC-supported MoFlo cell sorter and a VA-supported cell cytometer.

Recently, a VA-supported Histology and Imaging Core has been developed in this laboratory. The core includes a Nikon 80i microscope, a semi-automated Nikon 90i microscope and an inverted Nikon Ti microscope, all with epifluorescence and differential interference contrast capabilities and state of the art digital imaging systems as well as equipment for frozen and paraffin tissue processing.

Funding

Active Grants

- Ogawa: 1R01 DK 077821 “Hematopoietic Origin of Mesenchymal Cells”
- LaRue: VA Merit Review “Fracture Repair by Mouse and Human Hematopoietic Stem Cells” and VA Infrastructure Grant “Development of a Histology and Imaging Core”
- Mehrotra: 1K01 AR 059097: “Hematopoietic Stem Cell Transplantation in Osteogenesis Imperfecta” (To begin April 01, 2010)

Active Collaborative Grants in the Department

- Schulte: 1R01 DC 000713 “Inner Ear Iron Transport Mechanisms”
- Lang: Project 4 “Human Hematopoietic Stem Cells and the Aging Inner Ear” of 2 P50 DC 00422 (Dubno) “Experimental and Clinical Studies of Presbycusis”

Pending Grants

- Ogawa, Watson, LaRue (Multi PI Grant): 1R01 DK 090116 “Hematopoietic Stem Cell Origin of Connective Tissues”
- LaRue: 1R01 CA148772-01 “Hematopoietic Stem Cell-Derived Carcinoma Associated Fibroblasts in Tumor”



Chris Williams and Dr. Mehrotra.

Pathologic Diagnosis of Lung Cancer in the Molecular Age: Current Implications and Future Directions



*By: Ellen Riemer, M.D., J.D.
Assistant Professor, Pathology and Laboratory Medicine*

Lung cancer is the leading cause of cancer mortality worldwide. A lack of effective screening tools for early detection, the presence of smoking related comorbid illnesses, and the inherent molecular heterogeneity of the disease have all impeded efforts to improve outcomes for patients with lung cancer. Although many factors contribute to an individual patient's prognosis, recent clinical evidence indicates that clinicians can improve the prognosis for patients with advanced non-small cell lung cancer (NSCLC) by developing individualized treatment plans that target the underlying heterogeneous molecular pathways of tumor progression.

Over the past decade, great strides have been made in treating patients with NSCLC. Beyond histology, the study of predictive molecular markers provides additional data to help clinicians identify patients most likely to benefit from specific target therapies. Lung tumor samples obtained by biopsy often provide adequate material for molecular assays. Identification of these biomarkers has two primary roles: as a *prognostic* tool to help predict risk of recurrence or likelihood of survival (regardless of treatment received), and as a *predictive* tool to determine the likelihood of response or improvement from a specific therapeutic intervention.

New targeted therapies illustrate the importance of testing for molecular markers. Although EGFR, VEGF and K-ras mutations are already being tested for in diagnostic practice, other markers continue to be clinically tested and validated as a means of selecting the most appropriate treatment regimen. However, barriers remain to the widespread use of these markers as a adjunct to histologic evaluation. Questions linger about the reproducibility of results, as do concerns about accessibility (e.g., testing locations, financing) and convenience in terms of ease and invasiveness of obtaining samples for testing. Moreover, many targeted-therapies need more validation, and identification of the optimal set of biomarkers is still evolving and has yet to be determined. Additionally is the lack of standardization of technical methods in use for detection of molecular markers. All these factors will continue to play a role in the future expansion of the use of biomarkers in the tailoring of individualized treatment for patients with lung cancer.

As testing for specific biomarkers becomes more advanced, these tests will most likely be used to further customize treatment for patients with lung cancer. Currently, the most readily available test pertinent to the treatment of patients with advanced NSCLC is that for EGFR (epidermal growth factor) mutation and EGFR TKI (epidermal growth factor tyrosine kinase) sensitivity. Independent of treatment, EGFR mutation does not appear to be prognostic; however, it is predictive of patient's responses to EGFR TKI chemotherapeutic agents. Testing for K-ras mutations is also widely available today and used in current practice. The presence of a K-ras mutation is prognostic for poor survival, and studies have demonstrated poorer response rates to TKIs. Additional molecular tests have been developed to assess various other markers and sensitivities and have been shown to be strong predictors of patients' responses to certain medications. These include ERCC-1 for platinum-sensitivity, RRM-1 for gemcitabine-sensitivity, TS for pemetrexed-sensitivity, and beta III tubulin for sensitivity to taxanes/epothilones. However, these tests await further clinical testing and validation. Use of EGFR-, K-ras- and VEGF-targeted therapies are likely the tip of the iceberg in molecular diagnosis of lung cancer, as these are ushering in the age of personalized medicine, which will offer a subpopulation of patients more effective treatments.

Announcing MUSC's New Chromosomal Microarrays: A Wonderful New Tool for Genetic Diagnosis



By: *Daynna Wolff, Ph.D.,* Director, Cytogenetics and Molecular Genetics and *Iya Znoyko, Ph.D.,* Lead Technician, Microarray Section

Chromosomal analysis has long been a part of the testing paradigm for patients with unexplained mental retardation and autism spectrum disorders. Routine banding studies detect aberrations in about 2-3% of these individuals. Recently, the diagnostic yield has been greatly enhanced by application of DNA microarray studies that detect submicroscopic deletions and duplications in roughly 15-20% of patients.

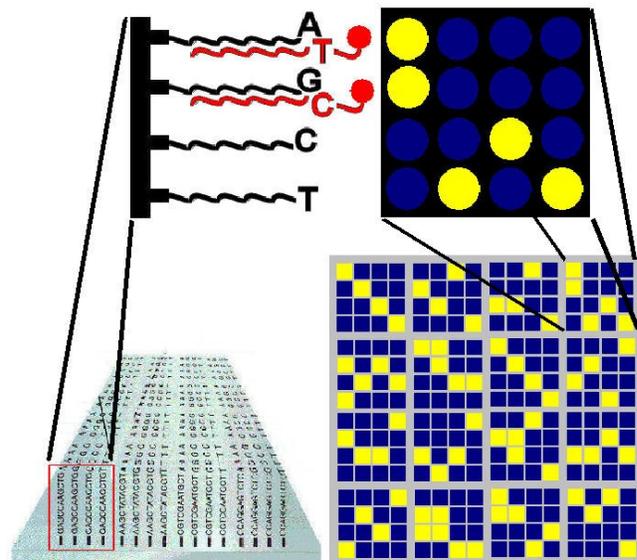
“With excellent unbiased, whole-genome coverage and a high density array of copy number markers, this test enables us to detect even the smallest submicroscopic aberrations, including those that would have been missed with classical cytogenetic techniques.”

The MUSC Cytogenetics Laboratory introduced our new Constitutional Microarray testing on January 1st, 2010. Constitutional microarray testing is indicated in any patient with a suspected chromosome imbalance, including those patients with unexplained developmental delay/mental retardation, dysmorphic features, autism spectrum disorders and/or multiple congenital anomalies. Our test utilizes the SNP (Single Nucleotide Polymorphism)-based Illumina BeadChip platform. With excellent unbiased, whole-genome coverage and a high density array of copy number markers, this test enables us to detect even the smallest submicroscopic aberrations, including those that would have been missed with classical cytogenetic techniques. The SNP microarray testing can reveal imbalances related to common microdeletion/microduplication syndromes, deletions or duplications in the gene-rich subtelomeric regions, as well as at thousands of loci throughout the genome. In addition, SNP microarray technology pro-

vides information about loss of heterozygosity (LOH), uniparental disomies (UPD), and offers insights into mechanisms associated with mosaicism and UPD.

While currently our testing is focused on application of this technology to interrogate the genome to look for constitutional copy number changes in patients with unexplained mental retardation and/or autism spectrum disorders, the potential for this testing in cancer diagnostic testing is just beginning to be appreciated. MUSC is a founding laboratory in the newly formed Cancer Cytogenomics Microarray Consortium. As a steering committee member of the Consortium, Dr Wolff is helping to establish clinical standards and guidelines for the use of microarray testing in cancer diagnostics. Additionally, the MUSC Cytogenetics laboratory is currently working on several research projects in the area of cancer. Stay tuned for more exciting developments in Cytogenetics!

SNP Array



National Lab Professionals Week

April 18-24, 2010



National Medical Laboratory Professionals Week provides the profession with a unique opportunity to increase public understanding of and appreciation for clinical laboratory personnel.

"Lab Week" which takes place the last full week in April each year, originated in 1975 under the auspices of the American Society for Medical Technology, now called the American Society for Clinical Laboratory Science (ASCLS). There are approximately 300,000 practitioners of clinical laboratory science in the United States. Since the development of this career group in the 1920s, the clinical laboratory science professional has played an increasingly vital role in the diagnosis and prevention of disease. Today, the clinical laboratorian is a key member of a health care team.

This year MUHA Laboratory Services will celebrate Lab Week through different events. In addition to the popular ice cream social sponsored by **Dr. Janice Lage** and

the hot dog/chili luncheon hosted by the lab managers, there will be some new offerings. **Rick Nolte, Ph.D.** will present a Snack and Learn where he will speak on "Hepatitis C Virus: Clinical and Laboratory Aspects of Infection." **Iya Znoyko, Ph.D.** will be featured at a Lunch and Learn and her topic will be "It's Not Science Fiction anymore: Microarray Genetic Analysis". Two areas of the laboratory will be in the spotlight during Lab Week. Our Fast Flow Lab will host afternoon tours to show off their Beckman Automation and new turn-around-time monitor. Tours will also be offered in Blood Bank and HLA. Blood Bank will feature the Galileo and electronic crossmatch and HLA will provide a glimpse inside DNA typing and crossmatching using the flow cytometer. There will something for everyone this year during Lab Week!



Histotechnology Professionals Day

March 10, 2010

Histotechnologists celebrated their first Histotechnology Professionals Day on March 10. Our histotechs, both in Histology and Mohs Lab, were very involved in promoting what they hope will be an annual event. Channel 5 came on site to film the histology lab and to conduct interviews with the staff.

Vinnie Della Speranza, Anatomic Pathology Manager, Wanda Smith, current president of SC Society for Histotechnology, and Chad McMahan, vice-president of SC Society for Histotechnology, met with Governor Sanford, to witness his signing of a proclamation, and to present him with a Histotechnology Professionals Day T-Shirt.

Congratulations to our Histology and Mohs Lab staff! Their efforts to promote their profession and raise public awareness of the service they provide daily to our patients were a great success.

State of South Carolina Governor's Proclamation

WHEREAS, histotechnology professionals are highly skilled scientific and technical personnel who play a vital role in the diagnostic process by preparing tissue samples for microscopic examination; and

WHEREAS, using their expert knowledge, histotechnologists work as part of a team in a variety of laboratory settings as veterinary, pharmaceutical and industry research scientists, anatomists, chemists and medical professionals; and

WHEREAS, histotechnologists are committed to continuing their education in order to maintain and improve standards of professionalism and keep up with evolving technologies and methodologies.

NOW, THEREFORE, I, Mark Sanford, Governor of the Great State of South Carolina, do hereby proclaim March 10, 2010, as

HISTOTECHNOLOGY PROFESSIONALS DAY

throughout the state and encourage all South Carolinians to recognize histotechnologists in the Palmetto State for their significant contributions to the safety of medical and research environments and the delivery of quality health care services to our residents.



A handwritten signature in black ink, which appears to be "Mark Sanford".

MARK SANFORD
GOVERNOR
STATE OF SOUTH CAROLINA



Residency Program Update

By: David Lewin, M.D., Residency Director



MATCH 2010

This year we interviewed 49 applicants out of 400 that applied for 6 open positions. We had a very successful match, filling all 6 positions. Below are the new residents that will start on July 1, 2010. I am very excited with our group of incoming residents!



Sarah Brooks
Louisiana State University School
of Medicine in New Orleans



Heidi Hendricker
Mercer University
School of Medicine



Jalidsa Pellicier
University of South Florida
College of Medicine



Julie Robinson
MUSC
School of Medicine



Christina Stallworth
University of Alabama
School of Medicine



John Wassum
Eastern Virginia Medical School

Chief Residents 2010 – 2011



ANNIE BARTLETT, M.D.



ANGIE DUONG, M.D.

Anne Bartlett, M.D. and **Angie Duong, M.D.** are the Chief Residents for 2010 – 2011 academic year. Congratulations Anne and Angie!

Jane K. Upshur, M.D., Post-Sophomore

Pathology Fellowship



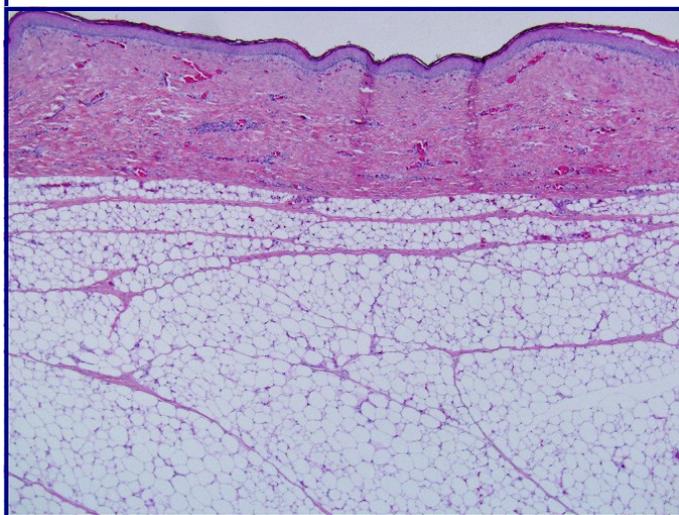
Ms. Sutton Boyd is our first Jane K. Upshur, M.D., Post-Sophomore Pathology Fellow. Ms. Boyd is a second year medical student at MUSC. She will spend a year with the department starting July 1, 2010, before completing her medical school studies.

Welcome Sutton!

Interesting Pathology Case of Quarter

By: Deborah V. Spencer, M.D.

An autopsy was performed on a 2-day-old male infant who was born at 28 weeks gestation age to a 31-year-old G1P1 mother. The infant weighed 865 grams and had flexion contractures of the upper and lower extremities, hypertelorism, retromicrognathia, and a fixed, widely open mouth. The skin was taut, thinned, and erythematous, with widespread skin sloughing and prominent subcutaneous blood vessels. A representative section of skin revealed hyperkeratosis, flattening of the rete ridges, thinning of the dermis with a paucity of adnexal structures, and slightly increased subcutaneous fat. Dermal collagen bundles were oriented parallel to the epidermis, and elastin fibers were virtually absent on Verhoeff Van Gieson (VVG) stain.



See answer on Page 17...

CONGRATULATIONS

to all the Pathology nominees
for the
2010 Faculty Excellence Awards!!!



Nick Batalis, M.D.
Asst. Dir., Residency Program



Sally Self, M.D.,
Dir. of Diagnostic Immunology

Dr. Nick Batalis

Dr. Debra Hazen-Martin

Dr. Erin Presnell

Dr. Sally Self

(Runner Up in the Second Year COM Faculty)

Dr. Jerry Squires

Dr. Jack Yang



Debra Hazen-Martin, Ph.D.
Assoc. Dean for
Curriculum Integration



Jack Yang, M.D.
Director of Cytopathology



Erin Presnell, M.D.
Director of Education



Jerry Squires, M.D., Ph.D.

Each year, students from the College of Medicine (Years 1-4) nominate clinical and research faculty for this award. An award ceremony is held annually to honor these faculty members with skits performed by the students and to announce the overall winners for each class. This event was held on Wednesday, April 7th, 2010.



Research Division Update

By: Bradley Schulte, Ph.D.
Vice Chair for Research

The Division of Research has had a busy and productive time from October through March. Twenty-three grant proposals were submitted requesting \$5,246,545 in total costs for the first year budget period. Also during this period, ten grants were awarded totaling \$1,154,095 over a one-year period (see table below). Congratulations, and thanks to all who participated in the effort to obtain these awards.

Principal Investigator	Title and Sponsor	Award Date/Amount
Nolte, Fredrick	A Clinical Evaluation of the FilmArray Respiratory Panel, 1T1 159 0002 SUBK/FA7014-08-C-0004, Idaho Technology/DOD Sub-Award	10/1/09 \$67,700
Wang, Yong	Radiation Biodosimetry, 0000680296/5 U 19 A1067770 FHCRC	12/1/09 \$110,625
Woolworth, Julie	COEE in Tobacco Related Malignancies: Abney Foundation Scholarship	12/1/09 \$25,000
Singh, Avtar	AMP Kinase Activity in Stroke Injury, 8042165, VAMC	1/1/10 \$125,000
Kawamori, Toshi	The Sphingolipid Pathway in Colon Cancer Chemoprevention, CA124687-01A2, NIH/NCI	1/1/10 \$306,063
Turner, David	ETS1 Expression as a Mechanism Mediating the Hormone Refractory Phenotype in Prostate Cancer IRG-97-219-11, ACS/IRG	1/1/10 \$30,000
Findlay, Victoria	Role of microRNA 510 in Breast Cancer Progression And Metastasis, IRG-97-219-11, ACS/IRG	1/1/10 \$30,000
Dammai, Vincent	Cellular Factors Promoting Renal Cell Carcinoma CA128002, NIH/NCI	2/1/10 \$277,400
Zhou, Daohong	Radiation-Induced Lymphoid and Hematopoietic Toxicity CA886860, NIH	2/1/10 \$147,832
Francis, Shimon	NRSA Pre-doctoral Fellowship (F31) to Promote Diversity DC010559, NIH/NIDCD	2/7/10 \$34,475
		Total = \$1,154,095

Research Division Update *(continued)*

Departures

We had several research personal leave us in the last quarter: Wei Feng, Vinu Jyothi, Honglang Li, Senthil Pazhanizamy, Lijian Shao and Lixian Wu all joined Dr. Zhou at the University of Arkansas. Romeo Abangan, Maan Li, Eishi Nishimoto and Anna Williams went on to other positions. Liya Liu transferred to the Hollings Cancer Center and Stacey Sigmon Moved to the Neuroscience division. We wish them all the best with their future endeavors.

Daohong Zhou, M.D., Associate Professor, moved to the University of Arkansas for Medical Sciences on March 1st where he was appointed as Professor of Pharmaceutical Sciences and was awarded the Winthrop P. Rockefeller Endowed Chair for Leukemia Research. At Arkansas, Dr. Zhou will serve as the Deputy Director of Radiation Health and build a research program in Radiation Biology. Daohong was a highly valued member of the Department for ten years. A drop-in was held on February 17th to thank Daohong for his service and see him off. We wish him all the best.



Arrivals

Joining us in March were Savannah Bandurraga, who joined Dr. Findlay's and Dr. Turner's lab as a Research Specialist; Darren Preece joined Dr. Watson's lab as a post-doctoral student; and Myroslawa Soloshchenko joined Dr. Spyropoulos' lab as a laboratory assistant.

Welcome to the Department!

Victoria Findlay, Ph.D. and **David Turner, Ph.D.**, both Research Assistant Professors in the Department, each received a highly competitive ACS IRG grant award to help them develop independent research programs in prostate cancer. Congratulations

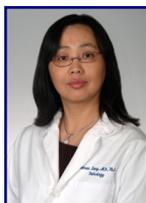


Vicky and Dave!

Julie Woolworth, Ph.D., a postdoctoral fellow working with **Omar Moussa, Ph.D.**, recently received a prestigious Abney Foundation Scholarship Award. In addition, Julie was awarded the Edith Peng Excellence in Research Award to support her travel to deliver a platform presentation at the American Association for Cancer Research Translational



Cancer Medicine 2010 Conference in Amsterdam. Way to go Julie!



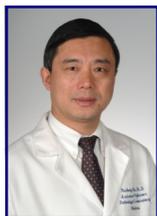
Hainan Lang, M.D., Ph.D. Gave an oral presentation on "Differentiation of Human CD34⁺ Hematopoietic Stem Cells into Glial-like Cells in the Injured Cochlear Nerve of a Humanized Mouse Model" at the 33rd Mid-

Winter Meeting of the Association for Research in Otolaryngology, Anaheim, CA, in February.

Also from Dr. Lang's Laboratory: 4 Poster Presentations were given at the Association for Research in Otolaryngology Meeting:

- Jyothi V, Li M, Kilpatrick L, Smythe NM, Zhu J, Schulte BA, Schmiedt RA, Lang H. Aggregation of Type I Unmyelinated Spiral Ganglion Neurons in Congenic Ly5.1 Mice. Presented by Vinu Jyothi.
- Kilpatrick LA, Li M, Jyothi V, Schmiedt RA, Fekete DM, Lang H. Adeno-associated Virus Transduction of the Adult Mouse Cochlea *in vivo*. Presented by Lauren Kilpatrick.
- Kilpatrick LA, Li M, Jyothi V, Goddard JC, Lang H. Role of SDF-1 Expression and Hematopoietic Stem Cells in the Injured Auditory Nerve. Presented by Lauren Kilpatrick.
- Li M, Jyothi V, Kilpatrick LA, Zhu J, Lang H. Expression of the Transcription Factor Sox2 in the Injured Cochlear Nerve of the Adult Mice. Presented by Maan Li.

Serum 25-hydroxy Vitamin D Test in Special Chemistry Laboratory



By: Yusheng Zhu, PhD, Director of Clinical Chemistry and Toxicology

Vitamin D is increasingly gaining recognition as a versatile agent that not only supports healthy bone formation and neuromuscular function but also plays a role in the development and progression of certain cancers, autoimmune disorders, infectious diseases, and many other conditions. Vitamin D deficiency is not uncommon. It has been estimated that 1 billion people worldwide have vitamin deficiency or insufficiency. According to several studies, 40 to 100% of U.S. and European elderly man and women are deficient in vitamin D. Because of the importance of vitamin D and its widespread deficiency, the orders for vitamin D tests have increased dramatically. In our hospital, vitamin D test volume doubles each year. In 2009, we sent 10,385 vitamin D tests to Mayo Medical Laboratory with a total cost of \$280,844.

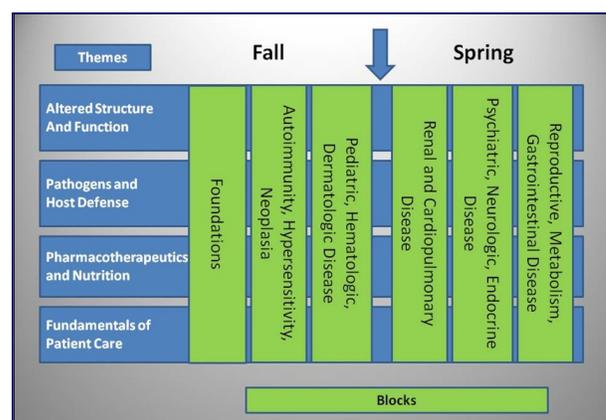
To meet this increasing clinical demand and to save cost for the laboratory, the Special Chemistry Laboratory in the Department of Pathology and Laboratory Medicine has successfully developed and validated a liquid-chromatography-tandem mass spectrometry method for the measurement of serum 25-hydroxyvitamin D. The methodology is the same as that used in Mayo Medical Laboratory. Our results (Y) show excellent correlation with Mayo results (X): $Y = 1.013X + 0.581$ ($r = 0.98$, $n = 102$). Therefore, the reference ranges remain the same. In addition, our mass spectrometry results (Y) demonstrated excellent overall agreement with results of the vitamin D radioimmunoassay (X) manufactured by DiaSorin: $Y = 1.06X + 1.10$ ($r = 0.95$, $n = 99$). The turn-around-time will be reduced from 5 to 2 days. Assuming annual sample volume is the same as last year, we will save the hospital approximately \$270,000 per year in referral laboratory charges.

COM 2nd Year Curriculum Update

By: Erin Presnell, M.D.,
Second-Year Medical School
Curriculum Coordinator



Efforts to reform the 2nd year curriculum are underway with several major tasks already accomplished, including the identification of 'Themes' to run throughout the year (replacing course designations) and the sequencing of curricular material into blocks, as illustrated below.



Theme leaders are as follows:

Altered Structure and Function: Drs. Erin Presnell and Nick Batalis

Pathogens and Host Response: Drs. Laura Kasman and Preston Church

Pharmacotherapeutics and Nutrition: Dr. John Hildebrandt (*still need a nutrition leader*)

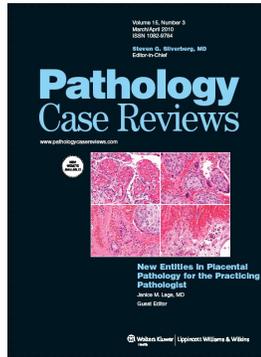
Fundamentals of Patient Care: Dr. Donna Kern

The theme grades (Pass, Fail, Honors) will appear on the students' transcripts. An Honors score within a block will be noted in the students' Dean's letters.

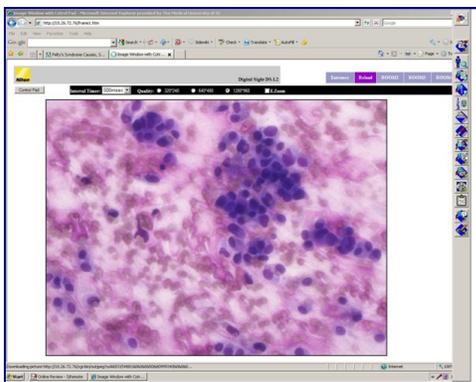
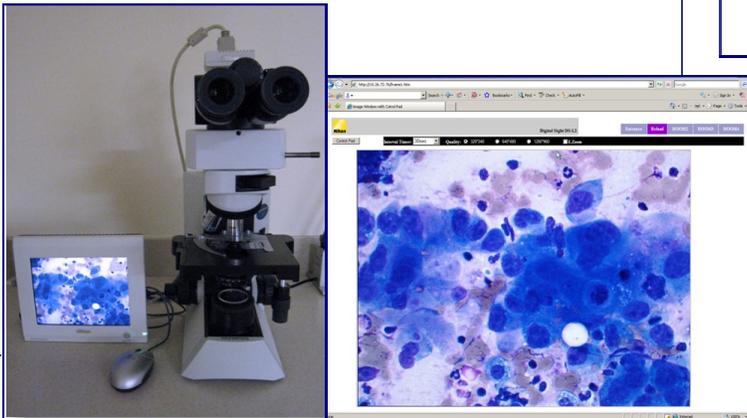
Block leaders (aka 'Block Heads') are still being finalized, but include Drs. Sally Self, Nick Batalis, Erin Presnell, Gene Burgess, Jeff Cluver, Ken Holden, Chris Robinson, Laura Kasman, and Gabe Virella with invaluable input from Dr. Hazen-Martin, Associate Dean for Curriculum Integration and Implementation in the Basic Sciences.

Around the Department....

Janice Lage, M.D., Department Chair, was a guest Editor for Pathology Case Reviews March/April 2010 issue. Drs. Nick Batalis and Laura Spruill were collaborators in the issue. The issue focused on New Entities in Placental Pathology for the Practicing Pathologist. New topics discussed include fetal thrombotic vasculopathy, meconium associated vascular necrosis, maternal floor infarction, congenital parvovirus B19 infection, and reviews of placental abruption and umbilical cord compression.



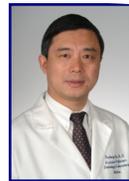
Mariam Alsharif, M.D. and Jack Yang, M.D., have a paper titled, "Telecytology for Immediate Assessment of Fine Needle Aspiration Cytology Specimens" accepted for publication in The Journal of Cancer Cytopathology. It pertains to our experience using telepathology (camera with microscope and an internet connection) to provide adequacy assessments and preliminary diagnosis for cytology and biopsy specimens performed at ART. (see pictures below)



Rick Nolte, Ph.D., received the **Excellence in Mentoring Award** from The Clinical Laboratory and Standards Institute. This award is given to the volunteer who enhances a mentee's performance, satisfaction and professional growth as a CLSI volunteer. Dr. Nolte also received the American Association for Clinical Chemistry (AACC) **Outstanding Speaker Award** for 2009, for achieving 4.5 or higher rating by participants at a clinical chemistry CME program. Congratulations Rick!



Yusheng Zhu, Ph.D. received the **Clinical Chemist Recognition Award** from the American Association for Clinical Chemistry (AACC) for demonstration of professional development through continuing education in clinical chemistry. Congratulations Yusheng!

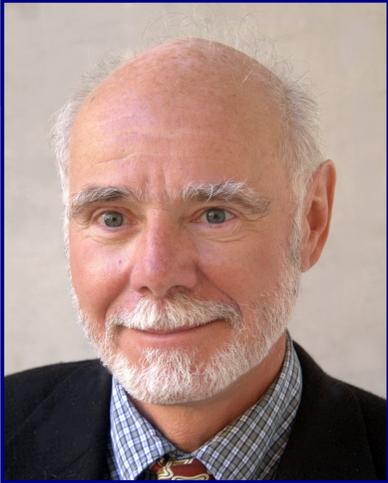


David Lewin, M.D., is currently the Chair of the Planning Committee for the 2011 Annual ASCP Meeting. Location will be Las Vegas.



Maria Gallego Attis, M.D. (on right) reviews cytology slides with cytopathology fellow, John Pham, M.D., pathology resident, Ford Rogers, M.D. and medical students Kendra Ferguson, Meagham Misiasz and George Magrath during daily cytopathology sign-out.

In Memoriam



Gian Re, Ph.D., Associate Professor in Pathology and Laboratory Medicine, passed away on January 16, 2010 at the age of 64. He was born in Gattinara, Italy, a small town in the Piedmont region of Northern Italy. In 1981, he became a permanent resident of the US and obtained his citizenship. He is survived by his wife, Barbara and his son, Jacopo Re. Dr. Re received a diploma of Scientific Maturity, Scientific Lyceum *Galileo Ferraris* in 1965 and a Ph.D. in Biological Sciences from the University of Turin, Italy in 1971. He had postdoctoral training in Dr. J.M. Kaper's Plant Virus laboratory at the USDA in Beltsville, MD. After several years as a researcher at the St. Jude's Children's

Research Hospital and at the MD Anderson Cancer Center, Dr. Re joined the Department of Pathology and Laboratory Medicine in 1992. Gian Re successfully collaborated with numerous Pathology research faculty and was an integral part of the molecular pathology clinical service, serving as director for several years, before assuming a role as the primary research and development leader. He will be fondly remembered for his gentle nature, his warm smile and willingness to help, his love of fine food and wines and his tales of fishing on the Folly pier. He will be missed by all who worked with him. Several colleagues have shared their thoughts below:

"He first worked under Dr. William Gerald to help develop molecular testing in the early days. He then worked with many other faculty in the department, most recently with Drs. Dayna Wolff, Denise Quigley, Debra Hazen-Martin, Brad Schulte and Rick Nolte. He is fondly remembered for his gentle nature, quick smile, and wry sense of humor. In spite of the ravages of polio, he never once complained about attending meetings anywhere on campus in spite of needing two crutches to get around. He loved good Italian wine, especially good Tuscan wines. We will miss Gian Guido and keep his memory within our hearts."

Janice Lage, M.D., Department Chair

"I worked with Gian for only a brief time at the end of his career here, but really enjoyed our interactions. We developed and evaluated several PCR-based assays together and I will miss his contributions to our molecular diagnostics lab. He was humble, always the gentleman, and, despite his physical disability, and later illness, was always upbeat with a wonderful sense of humor. The staff of the molecular diagnostic laboratory was genuinely fond of him and was greatly saddened by his passing. It fell to me to collect his belongings from the lab for his family after his death and the most difficult part was packing up the "Gone Fishing" sign that had hung for so long over his work area."

Rick Nolte, Ph.D., Vice Chair for Laboratory Medicine

"Gian Re had a strong background in molecular analysis of childhood cancers and we were especially interested in his help in studying the molecular basis of Wilms tumor. Gian was a master of the Northern blot, one of the most difficult and precise molecular biology procedures of the time, and could derive unbelievably clean and striking results from the minutest fragment of tumor or tissue culture. He made major contributions, as a result, to the detection of novel molecular changes in rare tumors that had previously proven impossible to analyze. Gian and William Gerald (now deceased) both worked on the Wilms tumor gene, WT-1. Later, when William returned to Memorial Sloan Kettering in New York, he discovered that the WT-1 gene was an integral component of the defect in the tumor which he had originally described as "desmoplastic round cell tumor of childhood." Gian was not only an expert investigator, but also a highly respected teacher, especially demanding of graduate students in their attempts to master Northern blot analysis. His pleasant personality and spirit of faculty citizenship was outstanding and he will be greatly missed."

Mark C. Willingham, M.D., Professor, Wake Forest University

and

A. Julian (Jerry) Garvin, M.D., Ph.D., Chair of Pathology, Wake Forest University



Spring 2010

Pratt-Thomas Symposium in Surgical Pathology and the McKee Cytology Seminar will be held on April 21-24, 2010 at Kiawah Island Golf Resort.

This year the **Pratt-Thomas Symposium** will focus on GI Pathology and Hepatic Pathology.

Invited speakers include:

Dr. Ken Batts, Abbott Northwestern Hospital

Dr. Mary Bronner, Director, GI Pathology, Cleveland Clinic

Dr. Larry Burgart, Abbott Northwestern Hospital Laboratory

Dr. Fatima Carneiro, Department of Pathology, Medical Faculty & IPATIMUP, Porto, Portugal

Dr. Larry Comerford, Division of Gastroenterology, MUSC

Dr. Robert Genta, Professor of Gastroenterology, University of Texas Southwestern Medical Center

Dr. John Goldblum, Chair and Professor of Pathology, Cleveland Clinic, Cerner College of Medicine

Dr. Joel Greenson, Professor of Pathology, University of Michigan Medical Center

Dr. John Hart, Professor of Pathology, University of Chicago

Dr. Gregory Y. Lauwers, Director, GI Pathology Services, Massachusetts General Hospital & Harvard Medical School

Dr. Audrey Lazenby, Director of Anatomic Pathology, Nebraska Medical Center

Dr. David Lewin, Professor of Pathology, MUSC

Dr. Elizabeth Montgomery, Professor of Pathology & Oncology, John Hopkins Medical Institutions.

The **McKee Cytology Seminar**, beginning Friday afternoon, will include invited speakers:

Dr. Edmund S. Cibas, Director of Cytopathology, Brigham and Woman's Hospital, Harvard University

Dr. Haytham Dimashkieh, Oconee Medical Center, Seneca, SC

Dr. Michael R. Henry, Mayo Clinic, Rochester, MN

Dr. M. Timothy Smith, Director, Anatomic Pathology, MUSC

Dr. Michael W. Stanley, United Hospital, St. Paul, MN

Dr. Patricia G. Wasserman, Chief, Cytopathology at North Shore - Long Island Jewish Health System

Dr. Jack Yang, Director, Cytopathology, MUSC.

Upcoming National Pathology and Pathology-related and Laboratory Medicine-related Meetings

April 17-21, 2010

AACR—American Association for Cancer Research
Washington, DC

April 24-28, 2010

ASIP—American Society of Investigative Pathology
Anaheim, CA

June 4-8, 2010

ASCO — American Society of Clinical Oncology
Chicago, IL

July 25-29, 2010

American Association of Clinical Chemistry
Anaheim, CA

September 26-29, 2010

CAP — College of American Pathologists
Chicago, IL

October 27-31, 2010

ASCP — American Society of Clinical Pathology, Annual Meeting
San Francisco, CA

December 8-12, 2010

San Antonio Breast Symposium
San Antonio, TX

Diagnosis to Interesting Pathology Case on page 10

Restrictive Dermopathy (RD, OMIM # 275210) is a rare, uniformly fatal genodermatosis in which taut, inelastic skin restricts fetal movements in utero, causing flexion contractures, abnormal facies, intrauterine growth retardation, and other manifestations. Although rare, the disorder has characteristic clinical and pathologic findings. The skin findings in RD include taut, thin skin with a thinned dermis, a paucity of elastin fibers, reduced or absent dermal appendages, and collagen bundles abnormally arranged in a configuration parallel to the skin surface.¹ The dermal-hypodermal border is also relatively straight² with slightly increased subcutaneous fat.³⁻⁴ RD is inherited most often in an autosomal recessive manner. The disorder is one of the laminopathies, resulting from defects in Lamin A, or defects in post-translational modification of Prelamin A, causing malformation of the nuclear lamina and changes in DNA replication and RNA transcription. RD has been linked with mutations in either the LMNA gene, which encodes four Type A lamin isoforms including Lamin A, or the ZMPSTE24 gene which encodes the zinc metalloproteinase which catalyzes the post-translational modification of Prelamin A to functional Lamin A.⁵⁻⁷

1. Smitt JH, van Asperen CJ, Niessen CM, et al. Restrictive dermopathy. Report of 12 cases. Dutch Task Force on Genodermatology. *Arch Dermatol*. May 1998;134(5):577-579.
2. Nijsten TE, De Moor A, Colpaert CG, Robert K,

Mahieu LM, Lambert J. Restrictive dermopathy: a case report and a critical review of all hypotheses of its origin. *Pediatr Dermatol*. Jan-Feb 2002;19(1):67-72.

3. Mau U, Kendziorra H, Kaiser P, Enders H. Restrictive dermopathy: report and review. *Am J Med Genet*. Aug 8 1997;71(2):179-185.
4. Wesche WA, Cutlan RT, Khare V, Chesney T, Shanklin D. Restrictive dermopathy: report of a case and review of the literature. *J Cutan Pathol*. Apr 2001;28(4):211-218.
5. Moulson CL, Go G, Gardner JM, et al. Homozygous and compound heterozygous mutations in ZMPSTE24 cause the laminopathy restrictive dermopathy. *J Invest Dermatol*. Nov 2005;125(5):913-919.
6. Levy N, Lopez-Otin C, Hennekam RC. Defective prelamin A processing resulting from LMNA or ZMPSTE24 mutations as the cause of restrictive dermopathy. *Arch Dermatol*. Nov 2005;141(11):1473-1474; author reply 1474.
7. Navarro CL, Cadinanos J, De Sandre-Giovannoli A, et al. Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of Lamin A precursors. *Hum Mol Genet*. Jun 1 2005;14(11):1503-1513.

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