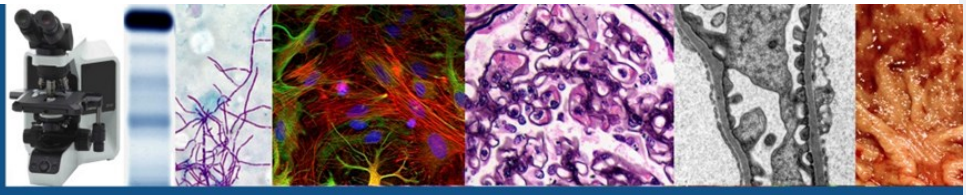
THE PATH WAY

March, 2014 **Volume 5, Issue 1**

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA



DEPARTMENT of PATHOLOGY & LABORATORY MEDICINE

Steven L. Carroll, M.D., Ph.D.

Inside this issue:

This is an exciting time to be a pathologist. Our discipline is in the midst of an evolution, with more advances occurring during the last five years than I saw in the previous 20 years. The rise of molecular pathology is a prime example of these changes and how they are markedly altering the way we diagnose a patient's disease and advise our clinical colleagues about the treatment of their patients. For decades, using a microscope to examine H&E sections has been our primary means of establishing a cancer diagnosis. I certainly don't expect the microscope to go away—it's a well-established technology that's backed up by years and years of pathology experience and, compared to many things we do in medicine, it's cheap. However, I do believe that in the near future, we are going to come to regard microscopic examination as simply the first step in the evaluation of a tumor; microscopic examination will instead be used to guide us to the molecular tests we will use to identify the driver mutations responsible for the tumor's pathogenesis and the relevant signaling pathways in our patient's tumor that should be targeted for personalized treatment. Obviously, the development of these approaches is going to raise a whole host of new challenges as we address issues such as the best practices for applying these new methodologies, determining how we store the extensive datasets these tests will produce and work with insurance companies to make sure that our patients can get these studies performed. These challenges are increasingly recognized nationwide in both academic medical centers and by our colleagues in private practice. This point was driven home to me very strongly when I recently attended the annual meeting of the American Foundation for Pathology and listened as other pathologists described their concerns about the implementation of molecular pathology in daily diagnostic work. These are obviously very important issues. However, it is also clear that molecular pathology is here to stay and I would argue that as an academic medical center, we have a special obligation to take the lead in advancing the use of this technology. At times, this is going to place us in somewhat "gray" areas where we question the proper use of the tests we are doing, how we communicate the results of these tests to our clinical colleagues and how we advise them in the care of their patient. Nonetheless, we have to bear in mind that access to this type of cutting edge technology is the reason why patients leave their community hospitals and seek out academic medical centers—we offer them a level of care and hope that they could not otherwise obtain.

It is also worth noting that academic pathology departments are particularly well suited to drive the development of new molecular pathology tests because our departments are also the homes of talented research faculty. Basic, translational and clinical investigators in pathology departments across the country are identifying and validating the clinical utility of the new molecular pathology tests that will increasingly be used in the workup of our surgical specimens. In coming years, I expect that this will fuel a growing synergy between research and clinical practice in academic pathology departments. I look forward to working with all of you as we shepherd through these changes in our own Department of Pathology and Laboratory Medicine and work to revolutionize patient care and defeat diseases such as the myriad cancers that plague humanity.

This newsletter is made possible from the generous contributions of MUSC's Pathology and Laboratory Medicine Faculty and Staff. The success of this publication is dependent upon this support. Thank you for your interest, time and information. For inquiries, suggestions or submission information please contact Lori Roten (roten@musc.edu).

Teacher of the Year Faculty Excellence – COM1 and COM2
Winner COM1 – Dr. Mike Caplan
Winner COM2: - Dr. Jerry Squires
Runner up – Dr. Nick Batalis

Each month and block the students of the College of Medicine like to honor the professors, residents, and physicians who they feel have been exceptional and have made an impact on their education for a *Teacher of the Block* & *Teacher of the Month* Award.

Dr. Nick Batalis won the Faculty Excellence Award for teaching 2nd year Medical Students in Block 4

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The Office of Development
YES CAMPAIGN
Changing What's Possible Through Giving.

Dear All,

The YES (Yearly Employee Support) Campaign has kicked off and runs through June 30th. I am fortunate to be on the Committee this year. This year's fundraising goal is $300,000.00. Your participation is very important. Every gift makes a difference. You should have received a campaign brochure in your mail slot. Please take some time to review the brochure and attachments. Thank you for making a difference!

Maxine T. Robinson
Forensic Operations Coordinator
Department of Pathology & Laboratory Medicine
(843) 792-3500
robinsma@musc.edu

MUSC Alert System

We want you to be aware of all emergency situations that impact the MUSC community!

Recently, MUSC implemented a new emergency management notification system, MUSC Alert, for the sole purpose of timely notifying faculty, staff and students of emergency situations that may impact the MUSC community. More information on MUSC ALERT and the link to manage your MUSC ALERT account can be found at www.musc.edu/muscalert. If you have specific questions or concerns about the MUSC Alert System, please contact Amanda Ritsema in the Department of Risk Management at 792-8514, or by email at ritsema@musc.edu .

Thank you,

Stewart A. Mixon
Chief Operations Officer
(P) 843.792.0888 (F) 843.792.1050
mixonsa@musc.edu

LAB SERVICES UPDATE

Faxitron BioVision is Here !

But What is it ?

Vinnie Della Speranza, Pathology Manager

No, it's not one of the invading Decepticon robots (like Megatron) here on earth in a battle to rule the universe (Transformers, the movie, 2007). Faxitron, a name well known to surgical pathologists, is a company that has been marketing surgical specimen x-ray machines to Surgical Pathology Laboratories for several decades.

The BioVision is the company's latest iteration, a portable, self-contained device that can provide high definition, digital radiographs of soft tissue tumors in about ten seconds. The instrument will be especially valuable in visualizing the location of tumor tissue in breast cancer lumpectomies and mastectomies prior to dissection which will not only provide a new revenue stream to the laboratory but will also reduce the number of tissue blocks that must be examined microscopically. The instrument, which costs $90,000, will pay for itself in about eight months.

Older generation units utilized x-ray film that had to be developed in a dark room. These were typically taken to the Radiology department's developing room but when Radiology went digital, Pathology was forced to abandon the old Faxitron technology because we simply had no way to develop the films.

The BioVision 's simple, one button operation allows the residents and attendings to operate the instrument with little training and the high resolution images are almost instantaneously obtained.

Images can be uploaded into the patient's CoPath record and could even be included in the pathology report if desired. For breast samples it even provides an opportunity to compare the specimen radiograph with the patient's mammogram.

The device will enable our pathologists to work up many soft tissue tumors with fewer paraffin blocks while enabling a more efficient and more accurate evaluation of surgical specimens.

Laboratory Education Programs

By: Nina Epps

- MUHA Histotechnology Program
  - Certificate in Histotechnology (HTL)
    - Hospital-based NCCLS accredited program
      - 2013 Class
        - » 4 Traditional students, 1 distance education student
          - MUHA = 100% pass rate (483 avg. score)
          - National average = 58% (421 avg. score)
      - Overall program stats
        - » Since 2007, MUHA pass rate = 92%
        - » Same time period, national average = 61%
      - Current Class
        - » 2 Traditional students, 1 distance education student (pending affiliation agreement approval)

- Medical Technology and MLT to MT Programs
  - Medical Technology
    - Current students
      - AASU Affiliation (subsidize tuition for 2 yr work agreement)
        - » 2 Current students
          - Graduate in December
      - New Model
        - » Clinical affiliation with AASU and other MT programs, but no tuition assistance
  - MLT to MT Programs
    - Provided resources for 8 MLT employees to obtain MT degrees

ODB Most Improved

Mining the Operational Data Base

Transfusion Service

Karen Garner, MHA, MT(ASCP)SBB
Manager – Transfusion Medicine/HLA

(4Q11-3Q12 vs. 4Q12-3Q13)

Total Expense

14% reduction

$124 to $107

per Case Mix Index (CMI) Weighted Lab Adjusted Discharge (Non MD, Area Wage Index (AWI) Adjusted)

(4Q11-3Q12 vs. 4Q12-3Q13)

Worked Hours

10% reduction

0.44 to 0.40

Hours worked per CMI Weighted Lab Adjusted Discharge
NOTE: CMI Weighted Total Facility Discharge volume increased by 10%

(4Q11-3Q12 vs. 4Q12-3Q13)

Wastage Expense

9% reduction

$2.1 to $1.9

per Unit of Dispensed Blood or Blood Product

(4Q11-3Q12 vs. 4Q12-3Q13)

Blood Expense

19% reduction

$100 to $81

per Case Mix Index (CMI) Weighted Lab Adjusted

CONGRATULATIONS!

Dr. Victoria Findlay & Dr. David Turner!

- **Dr. Yazhi Xing** (Lang's lab) won a travel Award from the International Association for Research in Otolaryngology
- **Lashardai Neniara Conaway** (a second year graduate student) was selected as an usher at this year's graduation
- **Dr. Demetri Spyropoulos** had 3 peer reviewed articles accepted for publication that his **Ph.D. student, Alexis Temkin,** worked on with him. He was the senior author on two of the publications
- **Dr. Yusheng Zhu's Clinical chemistry fellow, Satya Narla**, will give a talk , entitled "Evaluation of point-of-care (POC) glucose test accuracy performed by different operators" at the Association of Clinical Scientists and AACC Southeast Section joint meeting on May 31, 2014
- **Dr. Yusheng Zhu** has passed the Toxicology Board Examination administered by the American Board of Clinical Chemistry (ABCC) and become one of the 5 clinical chemists who are certified by ABCC in all 3 specialties: Clinical Chemistry, Toxicology, and Molecular Diagnostics

The CATALYST
Articles involving our Department

- **Title: Before bringing home that bacon(Dr. Dave Turner's Research) You can read the article at the link below:**

http://academicdepartments.musc.edu/Catalyst/archives/2014/1-10Bacon.htm

- **Title: Hearing research student shows promise in lab, leadership (Kayla Hill, 4th Year Graduate Student) You can read the article at the link below:**

http://academicdepartments.musc.edu/catalyst/archives/2014/3-21kayla.htm

The Importance of Patching and Updating Computer Software

By: Tony Eisenhart

We've all seen those pesky alerts when using our computers. Windows needs to install another update. The video drivers need another update. Even the antivirus software needs a daily update. While each of these is particularly frustrating considering the frequency in which updates are needed, they're an important element of any software experience.

Software patches serve a very important role beyond annoying computer users. Their intended purpose is to quickly push out fixes to bugs that may be occurring and create a safe computer environment. When you browse the internet, your computer is at the mercy of its current protective measures. Viruses, malware and rootkits are always on the search for security holes to exploit and gain entry to your personal data. While the best antivirus software would prevent this from ever happening, in order to accomplish such a goal you need to perform recommended updates.

The Microsoft Windows Automatic Update feature always sends you alerts of important updates when you're in the middle of something critical. These pop-ups ask you to allow the updates to be installed or even request a system reboot. The temptation is easy enough to ignore the update or cancel the shutdown. Your computer still works, so why bother ruining a good thing?
Simply put, software updates whether big or small are important. Much like with changing the oil in your car, brushing your teeth daily or going to a doctor for annual checkups, updates are necessary. Computers and the software they house require regular updates to ensure they continue to run safely and efficiently.

Viruses are ever-evolving, which too means your operating system, antivirus and other applications should continuously evolve as well. It's quite easy to ignore system updates for a while and fall behind the times, becoming vulnerable to new threats.

Updates serve a number of different functions as listed below:

- Fix security holes
- Optimize the utilization of resources on the operating system
- Add newer and more secure features
- Remove old and unprotected features

Update drivers to increase software efficiency
Patching is meant largely as a preventative measure rather than a curative one. While you may not always be aware of future or present threats, the developers who produce these updates make their livelihood in knowing about these risks.
Software patches and updates serve a very obvious function, despite how annoying their delivery vehicle may be. Keeping your software updated to the most recent version could save your computer and your personal information.

PATHOLOGY AND LABORATORY MEDICINE SUPPORTS MUSC

RECYCLING!

Recycling Guidelines for Labs at MUSC

Laboratory wastes, whether chemical or biological, can pose a significant risk to human health and the environment if not handled correctly. As part of MUSC's goal of becoming a sustainable campus, the MUSC Sustainability & Recycling Program provides collection service of recyclable materials. MUSC staff, students and faculty can reduce their impact on the environment and reduce costs.

WHAT CAN BE RECYCLED

Plastic, Glass & Metal:
Clean uncontaminated lab related plastic, glass and metal containers can be recycled in the blue container labeled "Plastic, Glass & Metal" These materials are collected once a week.

- Deface the label by marking a large red X across the name of the chemical
- "Triple-Rinse" containers that contained liquids, chemicals or media.
- Do not recycle containers that contained biohazard, noxious or highly toxic chemicals
- Place lids or caps back on whenever possible
  - **Plastic #1- #7:** Only rigid plastics: no Styrofoam, no plastic wrap are accepted
  - **Glass:** Clear & brown glass. No ceramics, No plate glass, No tempered glass like Pyrex are accepted
  - **Metal:** Metal trays (foil) and any item or container made of aluminum, steel or any other metal

Cardboard & Paperboard:
Flatten cardboard and paper board (tissue and gloves boxes…) and place it next to your trash container. Housekeeping collects all cardboard when they pick up your trash. The cardboard is then baled and recycled.

Paper:
Printer paper, envelopes and any other paper are recycled in the grey bin with a slotted green lid (23 gal.) All paper is shredded on campus. Paper is picked up once a week.

- Empty small desk side bins into the larger container

E-Waste & Batteries:
E-waste items include wires, plugs, empty toner cartridges and any other small electronic item; any large equipment (one with an asset tag) that you are disposing of must go to surplus. Collect e-waste in a box and batteries in a jug or a bucket. Call 2-4119 to request a pick up.

HOW TO RECYCLE

1. Decide what materials you will be recycling
2. email your questions to recycle@musc.edu
3. Request a bin for your area by calling 2-4119
4. Provide operator a contact name and room number where the bin will be located

MUSC ENGINEERING & FACILITIES Sustainability Program

Go Green

www.musc.edu/gogreen or email recycle@musc.edu

Recycle here

Rigid Plastics, Glass & Metal

Non-contaminated, clean, empty, triple-rinsed, "X" on labels

Plastic Containers:
pipette boxes, trays, centrifuge tube holders, sterile wipe containers, clean rigid plastics

Plastic Bottles:
soap, bleach, culture solution, betadine, ethanol, methanol, isopropanol, non-toxic dry chemicals, buffers and other clean bottles/jugs

Tools:
funnels, beakers, tongs, disposable cups…

Packaging:
Clean rigid plastic

Glass:
Unbroken glass bottles
NO plate glass
NO tempered glass (NO Pyrex)

Metal:
Aluminum cans & foil trays
Steel cans & containers
Tools & other metal items

MUSC ENGINEERING & FACILITIES Sustainability Program

Go Green

Full bin: call 2-4119; Questions: recycle@musc.edu or http://www.musc.edu/gogreen

RESEARCH DIVISION UPDATE

Statistics for the Division of Research from January through March.
Sixteen grant proposals were submitted requesting $3,704,468 in total first year costs.
Also, during this period eight grants were awarded totaling $1,496,550.

Congratulations and many thanks to everyone involved in obtaining these awards.

Bradley Schulte, Ph.D., Vice Chair of Research

SUBMITTED 1/1/2014 – 3/31/2014:

Steven L. Carroll, M.D., Ph.D.
Title: Prevention and Treatment of Neurofibromatosis Type-1 Associated Malignant Peripheral Nerve Tumors (Dr. Roth sub-award) $36,007 – Proposed Start Date 3/1/14

Victoria Findlay, Ph.D.
Title: A Novel Pre-clinical Strategy to Target the PI3K/ AKT Pathway to Overcome Resistance to HER2-Directed Therapy
$50,000 – Proposed Start Date 7/1/14

Victoria Findlay Ph.D.
Title: MicroRNA510 as a Biomarker of Response Platinum-Based chemotherapy $373,750 – Proposed Start Date 9/1/14

Kayla Hill
Title: Molecular Signaling of AMPK activation in Sensory Hair Cells via Traumatic Noise $52,806 – Proposed Start Date 4/1/14

Meenal Mehrotra, M.D., Ph.D.
Title: Regulation of HSCs and HSC-derived osteoblasts in osteogenesis imperfecta $373,750 – Proposed Start Date 9/1/14

Frederick Nolte, Ph.D.
Title: Abbott RealTime HCV Gt II Assay $63,732 – Proposed Start Date 1/1/14

Chandrakala Puligilla Ph.D.
Title: Mechanisms of Pattern Formation During Inner Ear Morphogenesis $373,750 – Proposed Start Date /1/14

Suhua Sha, M.D.
Title: Molecular Mechanisms in Noise-Induced Hearing Loss $368,750– Proposed Start Date 4/1/14

Avtar Singh, M.D.
Title: Efficacy of Redox-based GSNO Therapy in Stroke $373,750– Proposed Start Date 9/1/14

Avtar Singh, M.D.
Title: Mechanisms of Krabbe disease Pathobiology and Therapy $322,656– Proposed Start Date 4/1/14

Avtar Singh, M.D.
Title: Nitrosylation Mechanisms for Protection Against Neurovascular Inflammatory Injury $322,656– Proposed Start Date 5/1/14

David Turner, Ph.D.
Title: Glycation as a Mechanism Promoting Cancer Disparity $162,581– Proposed Start Date 4/1/14

Yong Wang, Ph.D.
Title: Targeting Cancer Stem Cells by a Natural Product-Derived Bmi-1 Inhibitor $224,250– Proposed Start Date 9/1/14

Yong Wang, Ph.D.
Title: Novel Strategies to Enhance the Efficacy of Lung Cancer Radiotherapy $186,874– Proposed Start Date 9/1/14

Dennis Watson, Ph.D.
Title: Differential Alternative Splicing and Gene Expression Stratifies Lung Cancer $194,906– Proposed Start Date 7/1/14

Je-seong Won, Ph.D.
Title: Nitric Oxide based Mechanism of Alzheimer's Disease $224,250– Proposed Start Date 9/1/14

RESEARCH DIVISION UPDATE, continued

AWARDED 1/1/2014 – 3/31/2014:

Hainan Lang, M.D., Ph.D.
Title: Experimental and Clinical Studies of Presbyacusis (Project 4/Dr.Dubno's P50) $245,911—Start Date 1/1/2014

Amanda LaRue, Ph.D.
Title: Hematopoietic Stem Cell-Derived Carcinoma Associated Fibroblasts in Tumor $236,305—Start Date 2/1/2014

Frederick Nolte, Ph.D.
Title: Abbott RealTime HCV Gt II Assay (corp. w/Hologic, Inc.) $63,732—Start Date 2/5/2014

Chandrakala Puligilla, Ph.D.
Title: Role of Sox2 in Specification of Prosensory and Hair Cell Fate in Mouse Cochlea $24,899—Start Date 12/1/2013

Brad Schulte, Ph.D.
Title: Experimental and Clinical Studies of Presbyacusis (Project 3/Dr.Dubno's P50) $181,463—Start Date 1/1/2014

Suhua Sha, M.D.
Title: Molecular Mechanisms in Noise-Induced Hearing Loss $355,596—Start Date 4/1/2014

Demetri Spyropoulos, Ph.D.
Title: Using Embryonic Stem Cells to Determine Potential Adverse Effects of Petroleum/Dispersant Exposure (Gulf of Mexico Alliance) $377,964—Start Date 1/1/2014

Dennis Watson, Ph.D.
Title: Building Next-Generation Bioinformatics cyberinfrastructure for Genomics-=enabled Research and Education in the Charleston Scientific Community (sub with C of C Dr. Anderson - awarded late) $11,680—Start Date 5/1/2013

In Remembrance:

Sharon Washington Mathis

She passed away in January, 2014. She worked as an Autopsy Transcriptionist in Pathology and Laboratory Medicine and retired after 30 years of service.

Jarvis Jenkins

Supply Specialist II

Nomination: Always willing to help.

Other Nominees: Eowyn Corcrain, Tony Eisenhart, Kevin Hildreth, Dolly Hope, Clint Infinger, Sonya Jordan, Teresa Kennedy, Linda McCarson, Carol Moskos, Tyrish Page, Katie Poston, Margaret Romano, Lori Roten, Nancy Smythe

ARRIVALS / DEPARTURES

ARRIVALS:

Blake Hays, joined Dr. Cheung's Lab as a Postdoc on March 31, 2014.

Qi Guo, joined Dr. Findlay's Lab as a Master Student on March 3, 2014.

Jody Longo, will join Dr. Carroll's Lab as a Staff Scientist I on April 7, 2014.

DEPARTURES:

London Penland, left Dr. Cheung's Lab as a Research Specialist I on January 2, 2014.

Christina Carrick, M.D., with Oconee Medical Center, left as a Staff Pathologist on January 31, 2014.

Haytham Dimashkieh, M.D., with Oconee Medical Center, left as a Staff Pathologist on February 7, 2014.

Lindsay McDonald, left Dr. LaRue's lab as a Postdoc on February 9, 2014.

Jianning Zhang, left Dr. Lang's lab as a visiting scholar on March 7, 2014.

INCOMING RESIDENTS & FELLOWS

RESIDENTS

Alexis "Alex" Elliot, M.D.
Katie Huenerberg, M.D.
David Lebel, M.D.
Charles "Charlie" Newman, M.D.
Emily Stuppi, M.D.

FELLOWS

Cytopathology
Matthew Bernstein
Heidi Hamilton, M.D.
Jalidsa Pellicier, M.D.

Dermatopathology—Courtney McFaddin, M.D.

Forensic Pathology—John Andrew (Andy) Wassum, M.D.

Hematopathology—Gregory Beaulieu, M.D.

Surgical Pathology – Clinical Instructors
Allen Flack, M.D.
Julie Robinson, M.D.

FAREWELL AND BEST WISHES!

Dr. Dimashkieh is now working for Greenville Health System in Greenville, SC.

Dr. Christina Carrick is now working for Greenville Health System at Oconee Medical Center.

FACULTY FOCUS

DENNIS WATSON, PH.D.

Dr. Dennis K. Watson is an established investigator with an international reputation in the areas of gene regulation and molecular oncology. He is currently Professor of Pathology & Laboratory Medicine and Biochemistry & Molecular Biology, as well as a Senior Scientist and member, Center for Oral Health Research (COHR) and leader of the Cancer Biology Division of the Molecular & Cellular Biology & Pathobiology Program in MUSC's College of Graduate Studies. From 2000-2013, he was the Program Leader, Cancer Genes and Molecular Regulation Program, Hollings Cancer Center. He is currently the Associate Director for Education and Training, Hollings Cancer Center.

Dr. Watson received his BS in Biology from the University of Southern California in 1972, and PhD in Cell Biology and Biochemistry from The Johns Hopkins University in 1980. After a postdoctoral fellowship at Johns Hopkins, he spent twelve years at the National Cancer Institute (NCI) in Bethesda and Frederick, Maryland where he rose from a staff fellow to a tenured research scientist. During the initial stages of oncogene discovery, Dr. Watson was the first to molecularly characterize the viral and cellular myc genes. While at the NCI, Dr. Watson was among the discoverers of the Ets gene family. He was directly responsible for the isolation and characterization of Ets gene products and their role in cellular proliferation, differentiation and etiology of cancer. In 1993, Dr. Watson joined the MUSC faculty as a tenured Professor. In addition to continuing to evaluate the role of specific Ets genes in development and cellular transformation, Dr. Watson has been responsible for the identification and functional characterization of genes with altered expression during cancer progression. His research uses in vitro and in vivo approaches to define the functional significance of altered gene expression and he continues to identify potentially novel therapeutic modalities.

Dr. Watson has published over 200 scientific articles and currently serves on multiple editorial boards. He has served on NIH, NCI, NSF, ACS, DOD and VA grant review committees as well as international panels. He is a member of American Society for Microbiology, American Association for Cancer Research, American Society for Cell Biology, American Association for the Advancement of Science, American Society for Biochemistry and Molecular Biology, Federation of American Societies for Experimental Biology and the American Society of Hematology. Dr. Watson has organized and led numerous scientific meetings, both nationally and internationally. He has trained and mentored over 25 predoctoral students, 25 postdoctoral fellows and 10 junior faculty, who now occupy key positions in academic and industrial laboratories throughout the world. In addition to mentoring, he has been a member of thesis committees for 44 graduate students.

In 2007, Dr. Watson became a member of the Cancer Biology Training Consortium which facilitates the exchange of ideas between individuals and institutions dedicated to the mission of training the next generation of cancer biologists. The Consortium works closely with over 60 institutions within the US and has established links with the NCI's Cancer Training Branch.

Dr. Watson's research focuses in two areas: (1) Molecular biology of gene regulation with a specific focus on the functional role of the Ets gene family of transcription factors during cellular proliferation and differentiation and transformation; and (2) Molecular genetics of cancer with emphasis on identifying and functionally characterizing genes critical for carcinogenic transformation, metastasis, and progression. Ets proteins activate or repress the expression of genes that are involved in various biological processes, including cellular proliferation, apoptosis, development, differentiation, senescence, angiogenesis, transformation, invasiveness and cancer progression. One Ets factor, PDEF, which is epithelial-specific, is reduced or lost in breast, colon and prostate cancer and its re-expression inhibits cell growth, migration and invasion. Analysis of Ets factor expression profiles in normal and cancer cells has demonstrated that a diverse combination of Ets family members is expressed at any one time. The multiplicity of Ets factors and their diverse roles indicate a possible "ETS conversion" mechanism of gene transcription which provides the cell with an integrated system by which the cells respond to and mediate the various intra- and extra-cellular signals that promote cell growth and migration. Among his current and future goals is to use state of the art next generation sequencing (RNA-Seq, ChIP-Seq, etc.) to understand the Ets regulatory network.

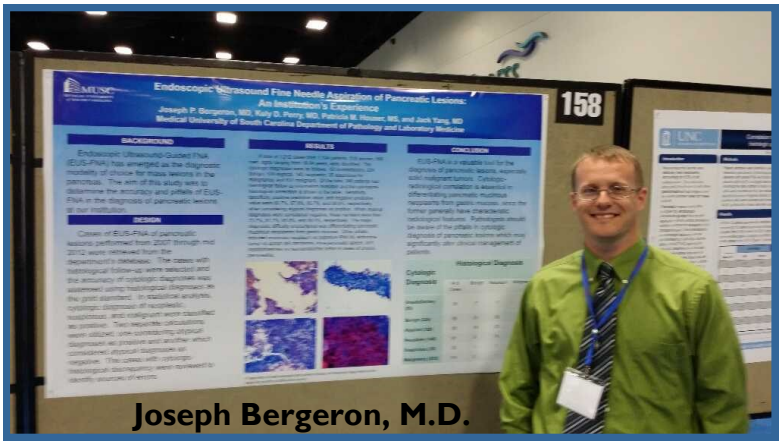
Other research projects are: the contribution of alternative splicing to cancer development and function of thromboxane synthase/ thromboxane receptor as targets for therapy and diagnosis of bladder cancer.

Dennis Watson and his wife Pat, also a scientist at MUSC, live in Mt. Pleasant with three labrador retrievers and a cat. They have two daughters and two grandchildren. Karen is the social worker for Developmental Pediatrics at MUSC and the mother of Ella and Ben. Victoria is a Doctor of Veterinary Medicine and currently a PhD student in Comparative Medicine at North Carolina State University in Raleigh, NC. Dennis enjoys reading novels, watching movies, and being outside when he is not working.

USCAP UPDATE

By: Tim Smith, MD

The United States and Canadian Academy of Pathology is the largest academic educational pathology society. The meetings are typically attended by 5000 academic pathologists from around the globe. The educational activities include proffered papers, posters, day-long courses, and shorter courses. Many of the USCAP members are also members of the many smaller companion societies which also meet simultaneously. The educational sessions of the meeting involve morning sessions, afternoon sessions, and evening sessions. This year the Department of Pathology and Laboratory Medicine was again well represented at the meeting. Two of the department's best trainees presented posters at the meeting. Dr. Jessica Forcucci, a second year resident, presented a series of very unusual entities in a poster titled "Myxoma of Bone." Dr. Joseph Bergeron, a cytopathology fellow, presented a poster titled "Endoscopic Ultrasound of the Pancreas, An Institution's Experience." Dr. Kirtesh Patel, a third year resident, attended the meeting as the department's representative to the College of American Pathologist's Resident Forum.



Joseph Bergeron, M.D.

Department faculty also attended and were involved in the national pathology community. Dr. David Lewin was invited to speak on massive juvenile polyposis at the Gastrointestinal Pathology evening session. Dr. Mary Richardson, who is the president elect of the North American Society of Head and Neck Pathology, organized that society's program on"Envisioning the next Head and Neck WHO Classification "Blue Book Wishes." Dr. Tim Smith, 12-year secretary / treasurer for the Association of Directors of Anatomic and Surgical Pathology, was asked to speak on "Adequate Staffing in a Post RVU Environment." These contributions were recognized by other attendees of the meeting as contributions from the MUSC Department of Pathology and Laboratory Medicine.

Jessica Forcucci, M.D.

UPDATES IN BREAST PATHOLOGY

By: Jonathan S. Ralston, MD

Guidelines regarding estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) biomarker testing in breast cancer have been recently updated to include the recommendations of the joint expert panel convened by the American Society of Clinical Oncology and the College of American Pathologists. As our understanding of breast tumor biology continues to evolve in this day and age of targeted therapy and personalized medicine, biomarker testing is more important now than it has ever been.

In 2010, it was determined that up to 20% of ER and PgR testing worldwide could be inaccurate (false positive or false negative), largely in part due to variation in pre-analytic variables, thresholds for positivity, and interpretation criteria. Given the impact of ER and PgR status on prognosis and the response to anti-estrogen therapies, standardized guidelines were developed. It is now recommended to test all newly diagnosed primary invasive breast cancers and recurrences for ER and PgR. In the case of multiple synchronous tumors, testing should be performed on at least one of the tumors, preferably the largest tumor. Similar guidelines were developed by the joint panel in 2013 for HER2. Additionally, for synchronous tumors of different histologic subtypes (i.e. ductal, lobular, etc.), it is often suggested to test each subtype. Studies have also demonstrated significant discordance between primary invasive carcinomas and metastases (lymph node or distant) from the same patient. The discordance between primary invasive carcinomas and metastatic disease has been documented concurrently at the time of initial diagnosis as well as following neoadjuvant therapy. Different theories are debated on how this occurs, whether it is from a clonal population of tumor cells that metastasized, “clonal selection” of therapy-resistant tumor cells following therapy, changes in the tumor cells secondary to therapy, or other. All of these theories seem plausible, and, in fact, each may likely contribute in individual cases. In any case, distant metastases (stage IV disease) should always be tested, and there may be some benefit of knowing the biomarker profile of regional metastases as well.

For both ER and PgR, testing is almost universally performed by immunohistochemistry, and it has been established that as few as 1% of tumor cell nuclei staining is a positive result. Patients with this degree of ER positivity have been shown to have a substantially and significantly better prognosis when treated with adjuvant endocrine therapy alone compared to those with <1% positivity. In studies retesting negative results in central laboratories, most falsely negative results had low positivity and were found to have poor fixation, negative internal controls, and/or absent internal controls. Current recommendations state that fixation of 6-72 hours in neutral buffered formalin with fixation initiated within 1 hour of the tissue procurement (cold ischemia time). Samples submitted outside of these time constraints, in other fixatives or solutions, or with a lack of internal controls or positive-staining thereof (intrinsic normal breast epithelium) should be considered uninterpretable if results are negative for receptor expression, and repeat testing should be considered on additional potential samples.

The expected results of a test based on the histopathology of the tumor should also factor into the decision of whether to retest additional samples of tumor. Examples would include tubular, lobular, and mucinous invasive carcinomas, or Nottingham grade I (well-differentiated tumors), almost always being ER and PgR positive. Should tumors of these phenotypes be negative on core biopsy, retesting the excisional specimen should be considered. Also, if a tumor is ER-/PgR+, retesting should be considered. Conversely, if a poorly differentiated (Nottingham grade III) tumor is negative for HER2, or a well differentiated tumor is positive for HER2, retesting of another tissue sample is recommended.

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In the 2013 updated HER2 guidelines, the duration of fixation was changed from 6-48 hours to 6-72 hours, similar to ER and PgR. For HER2, in situ hybridization is utilized as an alternative to IHC testing in tumor samples. Although other forms of in situ hybridization may be utilized, the most widely used and suggested method is fluorescence in situ hybridization (FISH) with a dual probe for HER2 and CEP17. Such probes allow for evaluation of cell ploidy as well as HER2 signal amplification. Additional changes to HER2 guidelines included changes to the positive, equivocal, and negative thresholds for both IHC and fluorescence in situ hybridization testing. For IHC, the positive (3+) threshold change from uniform intense membrane staining in >30% of tumor cells to circumferential uniform intense membrane staining in only >10% of cells. The equivocal category (2+) changed to include if >10% of cells display circumferential membrane staining that is incomplete and/or weak/moderate, or intense complete circumferential membrane staining in ≤10% of the tumor cells. For negative HER2 IHC, 1+ is now defined as incomplete membrane staining that is faint or barely perceptible within >10% of tumor cells, and a score of 0 is defined as no staining observed or ≤10% of the tumor cells display incomplete membrane staining that is faint or barely perceptible. Dual-probe in situ hybridization amplification is now defined as a HER2/CEP17 ratio ≥2.0 regardless of the HER2 copy number per cell, or a HER2/CEP17 ratio <2.0 with HER2 copy number of ≥6.0 signals per cell. Dual in situ hybridization equivocal is now defined as a HER2/CEP17 ratio <2.0 with HER2 copy number of ≥4 and <6.0 signals per cell. Dual in situ hybridization unamplified is now defined as a HER2/CEP17 ratio <2.0 with HER2 copy number of <4.0 signals per cell. At least 20 invasive tumor cells must be evaluated for ISH, and the entire slide should be examined for any population of cells >10% that displays increased HER2 signals/cell to be counted. In December 2013, our department switched from routinely performing HER2 by FISH on all invasive tumors with reflex to IHC if equivocal to performing concurrent IHC and FISH. Of 108 tumors examined by concurrent IHC and FISH, a total of 14 discordant results have been identified (12 cases with negative IHC found to be amplified by FISH, and 2 cases of

IHC positive tumors that were unamplified by FISH).

Indeed, it has been noted by previous studies that a small portion of tumors may demonstrate gene amplification by FISH but be negative for membranous protein expression by IHC, or show overexpression of membranous protein by IHC yet be unamplified by FISH. From our available cases to date, the results appear to reveal more HER2 positivity detected by FISH compared to IHC. Other studies have shown similar results. Nonetheless, we believe that the possibility of catching HER2 positivity that would otherwise be missed by testing with only be missed by testing with only one methodology first with reflex to the alternate methodology for equivocal cases warrants concurrent testing. These patients would potentially benefit from anti-HER2 therapy and have better prognosis and survival rates.

Questions that have yet to be fully answered concerning biomarker testing include whether or not there is any added benefit in stage I-III cancers of testing regional lymph node metastases as well as primary tumor at the time of diagnosis, or from testing regional lymph node metastases or primary tumor following neoadjuvant therapy. Such testing could reveal more tumor heterogeneity than previously believed and recent studies show some discordance between these samples, although the literature is relatively lacking in this area. Additionally, one may wonder if there is any added benefit of treating patients who display FISH amplification yet are IHC negative for Her2 with an anti-HER2 drug that targets intracellular HER2, such as Tykerb. Could there be intracellular HER2 that has been synthesized but not translocated to the cell surface? Future studies may help elucidate the answers to these questions.

References:

1. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med* 2010;134:e48.
2. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/college of American Pathologists clinical practice guideline update. *Arch Pathol Lab Med* 2014;138:241.
3. Aurilio G, Disalvatore D, Pruneri G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur J Cancer* 2014;50:277.
4. Ieni A, Barresi V, Giuffrè G, et al. Letter to the Editor regarding the paper by Aurilio et al., A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur J Cancer* 2014;50:1035.
5. Yang YF, Liao YY, Li LQ, et al. Changes in ER, PR and HER2 receptors status after neoadjuvant chemotherapy in breast cancer. *Pathol Res Pract* 2013;209:797.
6. Cho EY1, Han JJ, Choi YL, et al. Comparison of Her-2, EGFR and cyclin D1 in primary breast cancer and paired metastatic lymph nodes: an immunohistochemical and chromogenic in situ hybridization study. *J Korean Med Sci* 2008;23:1053.
7. van de Ven S1, Smit VT, Dekker TJ, et al. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. *Cancer Treat Rev* 2011;37:422.
8. Shafi H1, Astvatsaturyan K, Chung F, et al. Clinicopathological significance of HER2/neu genetic heterogeneity in HER2/neu non-amplified invasive breast carcinomas and its concurrent axillary metastasis. *J Clin Pathol* 2013;66:649.
9. Yao ZX1, Lu LJ, Wang RJ, et al. Discordance and clinical significance of ER, PR, and HER2 status between primary breast cancer and synchronous axillary lymph node metastasis. *Med Oncol* 2014;31:798.
10. Houssami N1, Macaskill P, Balleine RL, et al. HER2 discordance between primary breast cancer and its paired metastasis: tumor biology or test artefact? Insights through meta-analysis. *Breast Cancer Res Treat* 2011;129:659.
11. Raica M1, Cîmpean AM, Ceausu RA, et al. Hormone receptors and HER2 expression in primary breast carcinoma and corresponding lymph node metastasis: do we need both? *Anticancer Res* 2014;34:1435.
12. Arapantoni-Dadioti P1, Valavanis C, Gavressea T, et al. Discordant expression of hormone receptors and HER2 in breast cancer. A retrospective comparison of

The Cytogenetics and Molecular Pathology Laboratories Announce a New 26-gene Mutation, Massively Parallel Sequencing (MPS) Panel for Solid Tumors.

By Julie Woolworth, Ph.D.

This new 26-gene solid tumor cancer panel is being offered as the MPS service in our CAP- accredited CLIA laboratory. This assay contains many targeted oncology-related genes that are in compliance with various guidelines for targeted cancer therapies, including those identified by the National Comprehensive Cancer Network, College of American Pathologists, and Association for Molecular Pathology. Sequencing by MPS technology allows analysis of the 26 genes for up to 10 patients, with a 4-day procedure. The analysis will be performed using the Illumina TruSight Tumor panel on the Illumina MiSeq platform, which is currently the most successful and widely adopted technology. This test replaces the previous individual gene mutation tests for EGFR, KRAS, BRAF, and cKIT.

The 26-gene panel (listed below) is used to identify known genetic variants that guide selection of therapeutic treatment and variants that could identify patients for clinical trial enrollment. Specimens for this assay include formalin-fixed paraffin-embedded tumor tissue with a corresponding H&E stained slide that has been evaluated by a pathologist for sufficient tumor present at greater than 20% malignant cells. The assay is also validated for fresh tissue samples. All specimens will be batched and analysis performed once a week starting on Mondays; to be on the current week's run, specimens must be in the Molecular Pathology Laboratory by Mondays at 1pm. Current turn-around-time for the assay is between 5 and 10 days.

Gene	Exon	Gene	Exon	Gene	Exon
AKT	2	FGFR2	6	NRAS	1,2,3,4
ALK	2	FOXL2	1	PDGFRA	11,13,17
APC	15	GNAQ	4,5,6	PIK3CA	1,2,7,9,20
BRAF	11,15	GNAS	6,8	PTEN	1,2,3,4,5,6,7,9
CDH1	8,9,12	KIT	9,11,13,17,18	SMAD4	8,11
CTNNB1	2	KRAS	1,2,3,4	SRC	10
EGFR	18,19,20,21	MAP2K1	2	STK11	1,4,6,8
ERBB2	20	MET	1,4,13,15,16,17,18,20	TP53	2,3,4,5,6,7,8,9, 10,11
FBXW7	7,8,9,10,11	MSH6	5		

The lower limit of detection for this assay is 5% allele frequency, so the laboratory requests that all specimens have a tumor cell content of at least 15% to account for tumor heterogeneity. The average coverage for each amplicon in the panel is greater than 1,000X. The laboratory has determined that this technology cannot reliably detect mutations at coverage below 500X. Insertions or deletions over 25 bases in length are not detected by this assay. Individuals being analyzed should understand that rare diagnostic errors may occur. Possible sources of diagnostic errors can include genotyping errors from trace contamination of PCR, mosaicism at levels below standard detection, rare variants that can interfere with analysis, and from other sources.

Grant/research pricing for this test is available and includes variant analysis and interpretation. If interested in learning more, contact Julie Woolworth at 843-792-1181.

For more information on the Illumina sequencing technology, check out this short introduction http://support.illumina.com/training/courses/Sequencing_Illumina_Technology/index.html.

UPCOMING MEETINGS

PATHOLOGY SPRING SYMPOSIA

APRIL 28 , 2014 - MAY 5, 2014

AT

KIAWAH ISLAND GOLF RESORT

- **Experimental Biology Conference in San Diego, - 4/26 – 4/30**
- **Children's Tumor Foundation NF Conference in Washington, DC – 6/7 – 6/10**
- **American Association of Neuropathologists in Portland, OR – 6/12 – 6/15**
- **APC – Association of Pathology Chairs in Boston, MA – 7/8 – 7/11**
- **SNO - Society for NeuroOncology Meeting, November 13 - 16, 2014**

ALL HANDS MEETING

WEDNESDAY, JUNE 18, 2014 - 9:30-10:30 AM - HCC120

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