MUSC

DEPARTMENT *of* PATHOLOGY & LABORATORY MEDICINE

PATHOLOGY & LABORATORY MEDICINE NEWSLETTER

Volume 2, Issue 4 2011

Inside this issue:

Holiday Greetings and the Very Best Wishes for the New Year

From the Department of Pathology & Laboratory Medicine

www.musc.edu/pathology

Michael J. Caplan, M.D.
Golden Apple Teacher

The American Medical Student Association and the College of Medicine held the 2011 Golden Apple Awards Ceremony, November 30th. The Golden Apple Awards honor teaching excellence across the curriculum. This year the Golden Apple Award winners included Dr. Mike Caplan. Other distinguished teachers from the department were honored with award nominations

1st year: Golden Apple
Michael Caplan, MD

Pathology & Laboratory Medicine
2010-2011 Faculty Award Nominations:

First Year Class - Faculty Award
Dr. Michael Caplan
Dr. Debra Hazen-Martin

Second Year Class - Faculty Award
Dr. Sally Self
Dr. Jerry Squires
Dr. Paul Eberts, Chief Resident & Fellow

Clinical Years - Faculty Award
Dr. John Lazarchick

Congratulations to all of the teachers who upheld the traditional high standard of teaching excellence that MUSC is known for.

Dr. Michael Caplan at work with his typical smile.

Michael J. Caplan, M.D. Also Sweeps Teacher of the Month Competition

So it's not exactly news that Dr. Mike Caplan is an outstanding teacher; but if anyone thought he would be resting on his laurels, the first year medical students say otherwise.

According to Faculty Excellence Awards Representative Julie Teuber, "Dr. Caplan was the only professor this month to receive a nomination (over 50 of them!) from the first year students."

Some of their comments:

I would like to recognize Dr. Caplan from the College of Medicine. He helped many students along with myself in Anatomy lab. This was his personal time on the weekends and he was there for the students to put their minds at ease.

Definitely Dr. Michael Caplan. He is a fantastic teacher and deserves some recognition.

I would like to nominate Dr. Caplan as a teacher to be honored. He goes above and beyond his responsibilities to ensure that the students in the anatomy lab are well informed and prepared. I am sure this is not the only nomination that Dr. Caplan will receive, as all the 1st year students recognize his dedication.

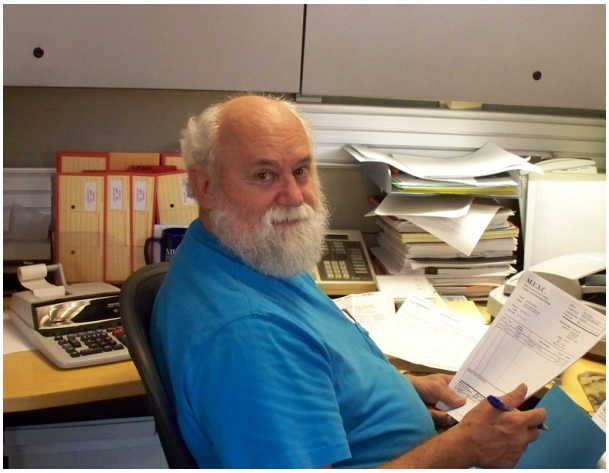
Dr Mike Caplan from COM. Best anatomy teacher ever!!

I›d like to recognize Dr. Caplan as out outstanding, dedicated, amazing teacher. He helped us COM1ers tremendously in gross lab to prepare for our practical this block. He was there all day Sat and Sun with us and went over the same stuff over and over as many times as necessary to ensure that everyone had a chance to review sufficiently. He went above and beyond the call of duty and we all want him to know how much we appreciated it. He should definitely be recognized with a teacher of the month nod at the very least.

DR. CAPLAN! I cannot believe this man's determination. He literally was in the anatomy lab from 9am to about 6pm BOTH days this weekend, not to mention he is in the lab for at least 2-3 hours a day EVERY weekend. I am so thankful to have such a great teacher.

NEWS FROM DEPARTMENT ADMINISTRATION & BUSINESS OFFICE

END OF AN ERA



Howard Vaughan Retires

"December 31st to most means the end of another year, but to the Academic Business Office it means the end of an era because this is when Howard Vaughan will retire. Howard has been with the Business Office for the last 23 years.

He began his career with the department in the shipping and receiving area. Howard's job was to receive shipments for the Department which included all the laboratories and offices. He was always willing to deliver shipments to wherever you needed them to go. After working in the receiving area, Howard transferred into the Academic Business Office where he has worked providing the very best service. He will be remembered the most for his smile and the kind words that he has had for everyone over the years. He was always willing to help no matter what the circumstance.

For me, he has always been my shadow right there every time I needed his assistance. I know that I will miss Howard more than anyone. I've had the pleasure of working with him my entire career here at MUSC. Miss him yes, but I would not want to change a thing. He has looked forward to this time for a year now telling me weekly how much time he had left. He looks forward to spending all of his time with his wife Brenda, traveling around and visiting with his friends. Let's just hope that he won't forget us for I know that I will not forget him. Goodbye old friend, it's been fun….."

by Howard's Supervisor and Good Friend,
Clint Infinger.

Howard and Brenda Vaughan

After 44 years in the Department of Pathology, Carol Moskos needs no introduction. Carol has long been synonymous with Electron Microscopy.
According to Carol, "I still enjoy looking at cell changes at the ultra-structural level"
"There have been a lot of changes in the department over the years, however the strong sense of family is still strong."
It's people like Carol that keep it that way.

Nomination cards can be found at each of the Department's MUSC Excellence Communication Board locations: 2nd floor Walton Research Building and 3rd floor Children's Hospital.
Drawing will be held at the next "All Hands Meeting" January 18, 2012 in room HCC 120.

New Hires:

Chandrakala "Kala" Puligilla, PhD
October, 2011 -Joins the "Auditory Neuroscience Group" in our research division working on cellular recognition and differentiation in the ear. Supported by NIH K99-R00

Jun Chen
Hired November, 2011 to work with Dr. Suhua Sha on her research project "Molecular Mechanism in Noise-Induced Hearing Loss."

Nancy Smythe
Transferred to our Research Division in November, 2011 from The Division of Basic Science. She is working in the Research Histology Lab, Electron Microscopy Recovery and Electron Microscopy Outreach Referral Recovery.

Lourdes Nogueira
Hired in December, 2011. She is working in our Research Division with Dr. Victoria Findlay and Dr. David Turner on two research projects; MUSC/Baylor Bridge Program and S.C. Cancer Dispanities Research Center

Retiring:

R. Howard Vaughan
Retiring December, 2011 after many years of service with the Department

Transferred Out of Department:

Joshua Kellner
Transferred to Biochemistry and Molecular Biology in the Division of Basic Science.

Departure:

Xia Xiao
Returned to China in October, 2011 after working with Dr. Yong Wang's research project

Savannah Bandurassa
Moved out of state in December, 2011

Fu-Quan Chen
Returned to China after working with Dr. Suhua Sha on her Research Project Molecular Mechanism in Noise-Induced Hearing Loss

SMOKEFREE

Countdown to MUSC
Being a Tobacco-Free Campus...

A message from Dr. Ray Greenberg, MUSC president

I am writing to share with you an important new policy that will be implemented soon on our campus. Acting upon the recommendations of the Student Government Association and the faculty senate, our board of trustees recently determined that MUSC will become a totally tobacco-free campus. In order to prepare adequately for this transition and to give faculty, students, staff, patients and visitors ample notice, the new policy will become effective March 1, 2012.

As South Carolina's academic health center and home to the only National Cancer Institute-designated cancer institute in the state, it is a part of our mission to prevent cancer and to lead by example in providing the healthiest environment possible for everyone on our campus.

This announcement is the first update as we prepare to become a tobacco-free campus. We will be offering smoking cessation classes and other available support and resources for our employees to encourage a healthier lifestyle. Please visit the smoke-free website at www.musc.edu/tobaccofree.

We look forward to your help and support in creating an environment that promotes wellness and healthy behavior.

IT Update by Tony Eisenhart

Social Network Web Site Usage Recommendations

Social networking sites such as Facebook, Twitter, MySpace, and LinkedIn have become extremely popular in the last decade. They're a great way to communicate with family and friends, share updates about your life, and stay "connected". However, you should be wary about how much personal information you, or your family members, post. Follow these simple suggestions when participating on social networking sites for a safe and enjoyable experience.

Privacy and security settings shouldn't be ignored or neglected: Learn how to use the privacy and security settings on social networks you are involved in. They are there to help you control who sees what you post and manage your online experience in a positive way.

http://twitter.com/privacy

http://www.facebook.com/help/privacy

http://www.myspace.com/pages/privacysettings

http://www.linkedin.com/static?key=privacy_policy

Use strong passwords: Make sure that your password is long, complex and combines, letters, numerals, and symbols. Ideally, you should use a different password for every online account you have. If you need to write down your password to remember it, store it somewhere away from your computer.

Once something is posted, it's always posted: What you post online stays online. Think twice before posting pictures, comments, or stories you wouldn't want your parents, children, or employer to see. Even when content is deleted or removed it can still be accessed.

Keep personal info personal: Be cautious about how much personal information you provide on social networking sites. The more information you post, the easier it may be for a criminal or someone else to use that information to steal your identity, access your data, or cause you harm.

Know and manage your friends: Some of the fun to be had when using social networking sites is creating a large pool of friends from many aspects of your life. That doesn't mean all friends are created equal, or need to be introduced to one another. Use tools to manage the information you share with friends in different groups. If you're trying to create a public persona as a blogger or expert, create an open profile or a "fan" page that encourages broad participation and limits personal information. Use your personal profile to keep your real friends (the ones you know and trust) more synched up with your daily life.

Be honest if you're uncomfortable: If a friend posts something about you that makes you uncomfortable or you think is inappropriate, let them know. Likewise, stay open-minded if a friend approaches you because something you've posted makes him or her uncomfortable. People have different tolerances for how much the world knows about them. Respect those differences. Post only about others as you would have them post about you.

Know what action to take: If someone is harassing or threatening you, remove them from your friends list, block them, and report them to the site administrator.

Be cautious and use sound judgment: Messages you receive on social networking sites that contain links, even links that look like they come from a trusted source can sometimes contain malware or be part of a phishing attack (attempts to collect personal information: logon and password and other identifying information by pretending to be a message form a friend or a business). If you are suspicious, don't click contact your friend or the business directly to verify the validity.

HIPAA

IMPORTANT HIPAA TIP

When sending emails, do not put any identifying information (patient name, MRN, etc…) in the subject line of the email. This is applicable for emails going both inside and outside the MUSC firewall. If you have a business need to identify the patient in the subject line, then just use the last four digits of the MRN.

If you have questions regarding this or other related privacy issues, contact the UMA Compliance Department at 876-1323 or compluma@musc.edu

The Division of Research has had a productive time from October through December. Twenty-five grant proposals were submitted requesting $4,908,721 in total first year costs. Also, during this period fourteen grants were awarded totaling $1,004,803 over a one-year period (see table below). Congratulations and many thanks to everyone involved in obtaining these awards.

Brown, Erica	Feasibility Study of Breast Cancer Candidate Genes in Three Population Groups in South Carolina (Internal Translational Pilot Project/Ford)	*8/1/11	$48,119
LaRue, Amanda	Circulating Fibroblast Precursors in Metastatic Sarcoma	*8/1/11	$70,000
Wolff, Daynna	Method Comparison & Clinical Specificity Study: Evaluation Of the Infinium HD Cytogenetic Abnormality Test (CYTO-001)	*8/1/11	$159,495
Wang, Yong	Role of miR-155 in Cellular Senescence and Lung Carcinogenesis (SCTR Award)	*9/21/11	$1,000
Turner, David	Biological Implications of DNA Glycation in Prostate Cancer Disparities (project 1/Dr. Ford's P20)	*9/22/11	$50,477
Brown, Erica	MUSC/Baylor Bridge Program (Neumann DOD)	*9/29/11	$48,303
Findlay, Victoria	MUSC/Baylor Bridge Program (Neumann DOD)	*9/29/11	$76,214
Wolff, Daynna	Evaluation of the Infinium HD Cytogenetic Abnormality Test Reproducibility Study (CYTO-002)	10/30/11	$21,150
Watson, Dennis	Contribution of Alternative Splicing to Lung Cancer Progression	12/1/11	$75,000
Puligilla, Kala	Role of Sox2 in Specification of Prosensory and Hair Cell Fate In Mouse Cochlea	12/1/11	$249,000
Steed, Lisa	GOM-11-MXGBS2/Repeat Inter-Laboratory Comparison Study for the BD MAX GBS Assay Migration to the BD MAX 6-Channel Platform	12/1/11	$7,538
Wang, Yong	Targeting the ROS-p38 MAPK Pathway as a Novel Strategy for Stem Cell Expansion	12/1/11	$165,007
Lazarchick, John	Safety & Efficacy of NNC 0155-0000-0004 in Prevention and Treatment of Bleeds in Pediatric Previously Untreated Patients with Hemophilia A	12/15/11	$33,500
		TOTAL	**$1,004,803**

* Award notifications were received in Oct/Nov of 2011 and start dates of grants were retroactive to the actual begin date on submissions.

Meet Jason Hope, M.D.
Cytopathology Fellow

My name is Jason Michael Hope and I am currently one of the cytopathology fellows at the Medical University of South Carolina. I was born in Heidelberg, Germany into a military family and spent most of my formative years traveling to different countries around the world. My family eventually settled in the small town of Raeford, NC and I attended East Carolina University for my Bachelor of Science in Biology and the University of Chapel Hill for medical school. I originally came to Charleston in 2007 for my combined anatomic and clinical pathology residency. I found Charleston and the pathology department to be like a home away from home and my second family. This warm and welcoming atmosphere played an critical role for me in deciding to pursue fellowship training at this prestigious institution. I choose the field of cytopathology because in today's market the clinician and patient's mantra is "more with less". The new age of medicine requires the need for minimally invasive procedures to provide as much ancillary information as possible and cytopathology is a perfect match. Whether providing molecular mutation analysis of lung malignancies or general thyroid nodule triage, cytopathology's future is bright entering into the 21st century.

In my free time, I enjoy reading novels, bowling, and trying out the latest techno gadgets. I am currently reading several classics, courtesy of the android market on my tablet.

My future career goals are currently in development, but I would like to work and live somewhere in the southeast (if the job market permits) and have a role in the education of future pathology residents.

BREAST PATHOLOGY UPDATE
by John Metcalf MD

Concurrent with the opening of Ashley River Tower (ART) in 2008 and the transfer of surgical oncology services to the facility later that year, the surgical pathology service was reorganized to accommodate subspecialty signout of breast cases (as well as GI and some pulmonary cases). The advantage of moving the breast service to ART was that it placed the grossing and microscopic examination of breast tissues in close proximity to the operating rooms and enhanced communication between pathologists and surgeons. In addition, subspecialty signout enabled those surgical pathologists involved in the breast service (Drs. Rumboldt, Ralston, and Metcalf) to subspecialize and to develop additional expertise in breast disease so that they could be better equipped to actively participate in the rapidly evolving multidisciplinary field of breast cancer diagnosis and treatment.

Although the numbers of "in house" breast biopsies and surgical procedures has remained relatively stable (~2000 total per year) since 2009, increasingly breast patients are referred to the Hollings Cancer Center from other institutions for evaluation and advanced oncologic care. This has resulted in an increasing number of surgical pathology consultations (more than 200 this year through November) with the original histologic material being reviewed and with ancillary testing (hormone receptors, Her2, etc) performed as necessary.

John Metcalf M.D.

MUSC Department *of* Pathology & Laboratory Medicine

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

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

FOCUS ON THE FINDLAY LAB
by VICTORIA FINDLAY PhD


Dr. Victoria Findlay

The primary interest in our lab is the role of microRNAs in breast cancer progression and metastasis. Breast cancer is the most frequently diagnosed malignancy and the second leading cause of cancer deaths in American women, second only to lung cancer. This year, an estimated 178,480 new cases of invasive breast cancer will be diagnosed among women, as well as an estimated 62,030 additional cases of in situ breast cancer in the US, resulting in approximately 40,460 deaths. In fact, every 68 seconds a woman dies of breast cancer worldwide. Breast cancer mortality is almost invariably attributable to metastasis that is clinically untreatable despite aggressive chemical and radiation therapies. Additional studies directed towards elucidation of the factors involved in progression should facilitate the design of molecularly based diagnostic and therapeutic approaches. The 5 year survival rate of localized disease is 98%, however this percentage drops dramatically to 26% in patients with metastatic disease. Therefore, understanding the pathways and processes that are involved in metastatic progression is of the utmost importance to prolong survival in breast cancer patients.

MicroRNAs

MicroRNAs (miRNAs) are endogenous 19-25 nucleotide RNAs that have emerged as a novel class of small, evolutionarily conserved gene regulatory molecules involved in many critical developmental and cellular functions. miRNAs base-pair with target mRNA sequences primarily in their 3' untranslated region (3'UTR). Through specific base pairing, miRNAs induce mRNA degradation, translational repression, or both depending upon the complementarity of the miRNA to its mRNA target. Each miRNA can target numerous mRNAs, often in combination with other miRNAs, therefore controlling complex regulatory networks. It is estimated that there are ~1000 miRNAs in mammalian cells, and that about 30% of all genes are regulated by miRNAs. Over 3,000 identified mature miRNAs exist in species ranging from plants to humans, suggesting that miRNAs are ancient players in gene regulation. Their existence and conservation throughout species supports the concept that they perform critical functions in gene regulation. Indeed, the conserved evolution of both miRNAs and transcription factors highlights their importance in and the complexity of gene regulation.

MicroRNAs as a New Class of Oncogene and Tumor Suppressor

What makes miRNAs particularly important is their involvement in most, if not all, fundamental biological processes. Mounting evidence indicates that miRNAs may also play a significant role in cellular transformation and carcinogenesis acting either as oncogenes or tumor suppressors (**Figure 1**). Furthermore, specific miRNA signatures have been identified for both solid cancers and hematologic malignancies (**Figure 2**). Intriguingly, mounting evidence suggest that the power of miRNAs lies in the ability to distinguish specific cancer subtypes based on their miRNA profile, including, and of direct relevance to our studies, breast cancer.

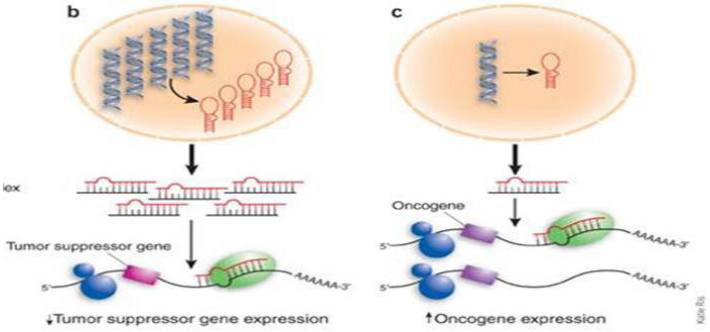


Figure 1: **A model of miRNA involvement in cancer by modulation of expression of tumor suppressor genes and oncogenes. (b)** Overexpression of miRNAs - for instance, by amplification of the miRNA-encoding locus - could decrease expression of the target, such as a tumor suppressor gene. (c) Underexpression of miRNAs - for instance, by deletion or methylation of the miRNA locus - could result in increased expression of a target such as an oncogene. Figure and legend are adapted from Caldas and Brenton, 2005.

Our published studies show elevated levels of miR-204 and miR-510 in human breast tumor samples when compared to matched non-tumor controls. In addition, over-expression of miR-204 & -510 in immortalized non-transformed and non- invasive breast cancer cell lines results in increased migration, invasion, cellular transformation and an altered morphology similar to that seen in cells undergoing Epithelial-Mesenchymal-Transition (EMT) (**Figure 3**). Down-regulation of the epithelial marker E-cadherin and up-regulation of the mesenchymal markers uPA and Slug are observed in these cells and the Ets transcription factor family member, PDEF (prostate-derived Ets factor), was

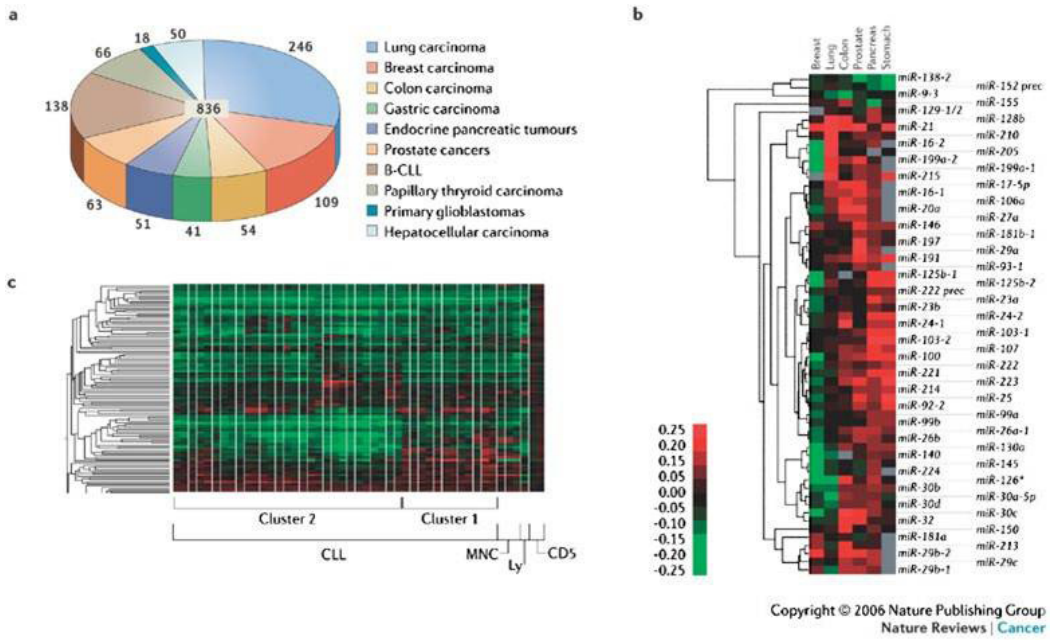


Figure 2: MicroRNA signatures in Cancer. Adapted from Calin and Croce, 2006.

identified as a direct miR-204 & -510 target. Interestingly, miR-510 is located on chromosome Xq27, a region that is reported to be associated (amplification) with breast cancer. We have been involved in the identification of downstream targets of miR-510 as well as the elucidation of the upstream signaling pathways that are involved in its activation in order to better understand the role of this miRNA in the promotion of breast cancer. To date, no other studies have identified a role for miR-510 in cancer. miR-204 is located on chromosome 9q21, a region that is reported to be amplified in cancer. While few studies have investigated miR-204 in cancer, a microarray study revealed that miR-204 levels were significantly elevated in 14 of 20 breast cancer samples compared to normal control. In addition, a recent study showed that positive lymph node status in melanoma patients was characterized by a statistically significant elevation of miR-204 levels, suggesting a possible role for miR-204 in the metastatic process. In collaboration with Dr Jeffrey Rosen (Baylor College of Medicine, Texas) and the Breast Cancer Focus Group here at MUSC, we will build on our preliminary data to further evaluate the role of miR-204 as an oncomir in breast cancer initiation, progression and metastasis.

Unfortunately, there are not many successful treatments in the clinic for women who present with metastatic disease. In addition, the 5 year survival rate for these women is very low. The significance of our work is its potential to contribute important new understanding to the genetic basis of multi-step tumor development and disease progression. The presence of specific miRNA expression may also provide another much-needed indicator of metastasis. Data collected by the SEER (Surveillance, Epidemiology, and End Result) program of the US National Cancer Institute (NCI) showed that less than 10% of breast cancer patients had detectable distant metastases at diagnosis. These facts argue that interruption of the metastatic process could be useful for a majority of individuals with breast cancer. The ultimate long-term goal of our lab is to identify novel targets of miR-204/510 that may be therapeutically targeted in breast cancer patients with invasive and/or metastatic disease with the objective to prolong survival and/or inhibit metastatic progression.

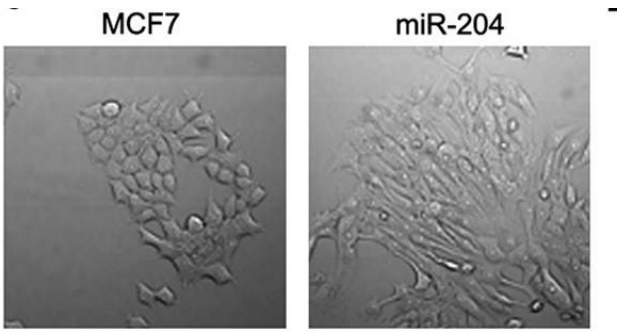
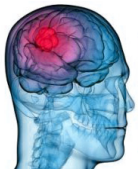


Figure 3: miR-204 over-expression (right panel) induces an epithelial-mesenchymal transition in non-invasive MCF7 breast cancer cells. Control epithelial cells are shown in the left panel.



Recent Advances in Brain Tumors

By Cindy A. Welsh, M.D.

Many different types of tumors, benign and malignant, have been identified in the central nervous system (CNS). The prognoses for these tumors are connected to clinical features, such as the age of the patient and the location, as well as the histology of the tumor. In adults, about half of all CNS tumors are malignant, whereas in pediatric patients, more than 75% are malignant. The distribution of CNS tumors by location has remained constant for many years, but there has been a slight increase in more malignant tumors over the past decade. Arising from glial cells, gliomas represent over 36% of all primary CNS tumors and consist of astrocytomas, oligodendrogliomas, ependymomas, and mixed gliomas. The most common gliomas are astrocytomas, and these tumors are classified by the World Health Organization (WHO) into Grades I through IV. Grade IV, the highest grade of astrocytoma, includes glioblastoma (GBM). GBM is the most common malignant primary CNS glioma in adults (about 51% of CNS gliomas). GBM is unfortunately the most difficult to effectively treat and has the worst patient survival, although these survival numbers have been recently improving.

Many of the histologic patterns characteristic of gliomas now have an explanation through cytogenetics and molecular studies. They have been shown to also contain the beginnings of therapeutic possibilities for the future. Over the last two decades, correlation of histology, which has been documented since the early 1900s, with the genetic changes and molecules responsible for the histology, has led to important advances in our understanding of the classification, diagnosis and etiology/pathogenesis of brain tumors and to pay off in terms of new possibilities for treating gliomas. Although important advances continue to be made in traditional clinicopathological (morphological) study and immunohistochemistry, the greatest breakthroughs have been in molecular pathology and genetics. Some of the problems with effects on grading due to issues with sampling of tumors may be overcome by molecular studies. We currently send out for FISH for 1p and 19q deletions in oligodendrogliomas and mixed oligoastrocytomas, as this has been shown to be of prognostic significance, and have treatment implications. DNA microarrays are becoming more and more common in tumor testing, including brain tumors, for separating out prognostic and treatment related groups. This is currently performed at other institutions as part of clinical trials in which our GBM patients are being enrolled. Isocitrate dehydrogenase 1 gene (*IDH1*) or protein testing can help us determine whether our patients have a glial neoplasm or reactive gliosis, because these changes are not seen in gliosis. At MUSC we chose to perform immunohistochemistry for IDH1 rather than molecular testing. The most common astrocytoma in the pediatric age range is the pilocytic astrocytoma. The molecular biology of pilocytic astrocytomas (PAs) differs according to location, yet BRAF rearrangements which provide useful information in some systemic tumors, do not appear to produce PAs with different behavior. Because clinical outcome is independent of BRAF status, we are not currently testing for BRAF in pilocytic tumors. Not all of the advances in treatment of brain tumors have been in the realm of malignant tumors. Understanding of the involvement of mTOR molecular pathways in Tuberous Sclerosis has led to treatment for subependymal giant cell tumors (SEGA) with everolimus.

The most common malignant primary CNS tumor in pediatric patients is medulloblastoma. New evidence indicates that the various cell populations that form the cerebellum and the cell signaling pathways that regulate cerebellar development probably represent distinct compartments from which the different subtypes of medulloblastoma arise. It is expected that definitive characterization of each subtype will improve treatment. Currently we can use immunohistochemistry for beta-catenin, and a silver stain which precipitates out on reticulin to confirm subtypes in medulloblastomas. Another tumor in the differential diagnosis (particularly in very young children) is the atypical teratoid/rhabdoid tumor. When this entity is under consideration, several immunostains can help to increase the suspicion. Definitive testing can then be done for INI1 through several avenues, including FISH, RT-PCR and immunostains. This testing is currently sent out from MUSC when necessary to confirm the diagnosis of rhabdoid tumor.

One of the challenges in oncology is developing better therapies for preventing and treating metastases to the brain. Recent research is changing the understanding of brain metastases. Previously, the occurrence and poor outcomes associated with brain metastases had been largely attributed to the exclusion of anticancer drugs from the brain by the blood–brain barrier (BBB), but studies in multiple tumor types have demonstrated that brain metastases have significant molecular differences from primary tumors and extracranial metastases. These molecular differences may not only promote the formation of brain metastases, but they may also contribute to these tumors' poor responsiveness to therapies. Such changes may be intrinsic to the cancer cells or driven by unique interactions with the brain microenvironment. An improved understanding of the molecular characteristics of brain metastases that contribute to their aggressive behaviors will assist the development of cogent successful treatments for these tumors. Currently, we can test brain metastases from pulmonary tumors by RT-PCR for EGFR, KRAS, and BRAF; as well as FISH for ALK.

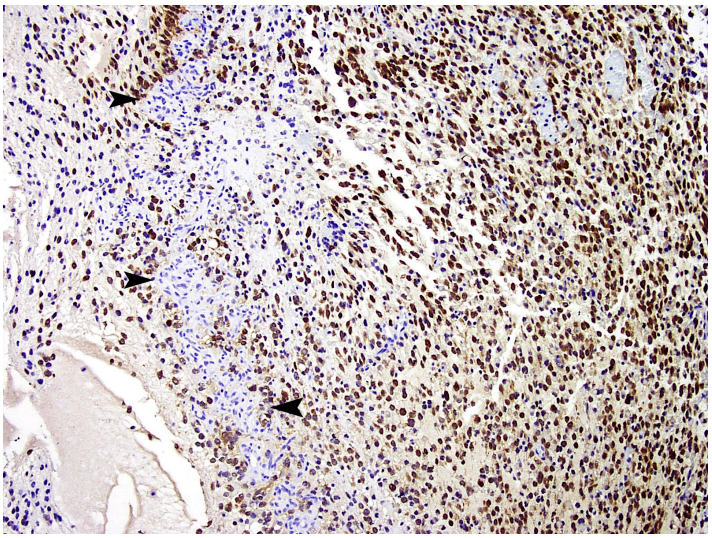
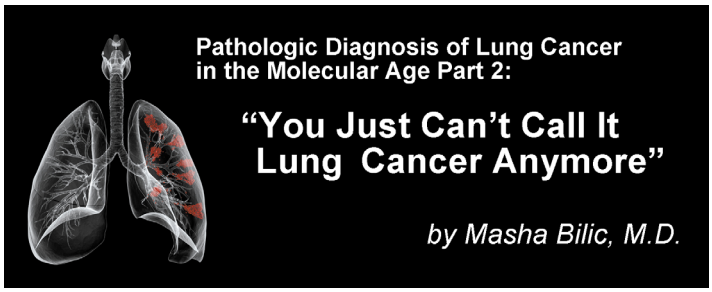


Figure 1. GBM with oligodendroglial component demonstrating positive staining of tumor cells and by contrast highlighting the negative cells of the complex microvascular change (arrows).

The World Health Organization (WHO) classification of central nervous system (CNS) tumors is in its 4th edition with the publication of the *WHO Classification of Tumours of the Central Nervous System*. The 4th edition has introduced a substantial number of changes to the previous edition that reflect both the recognition of new brain tumor types and a more current understanding of neoplastic behavior. There is a new introductory chapter titled, ''WHO Grading of Tumours of the Nervous System.'' which explains that the histologic grade, as used by WHO, is meant to communicate a ''stage of malignancy'' that will predict biologic behavior. The 4th edition has introduced 7 changes in the grading of CNS neoplasms from the 3rd edition, some of which are minor and some of which have substantial implications. Anaplastic oligoastrocytomas with necrosis are now designated glioblastoma with oligodendroglial component, WHO grade IV. Brain invasion by a meningioma is now an independent criterion for WHO grade II. Criteria have now been defined for atypical choroid plexus papilloma with a designation of WHO grade II. Pineocytomas are now classified as WHO grade I; pineal parenchymal tumor of intermediate differentiation as WHO grade II or III; and pineoblastoma remains WHO grade IV. Gangliogliomas: are now classified as WHO grade I or III; the grade II designation has been eliminated. Cerebellar liponeurocytoma is now designated WHO grade II tumor as the behavior of this tumor has been followed for a longer period of time. Criteria have been established for distinguishing anaplastic hemangiopericytoma, WHO grade III from hemangiopericytoma, WHO grade II .New entities include angiocentric glioma (WHO grade I), pituicytoma (WHO grade I), spindle cell oncocytoma of the adenohypophysis (WHO grade I), papillary glioneuronal tumor (WHO grade I), and rosette-forming glioneuronal tumor of the fourth ventricle (WHO grade I).



What's so wrong with the term bronchioloalveolar carcinoma (BAC) that someone would want to make it extinct? Nothing really, except that it seems to raise confusion among pathologists and clinicians alike. If you asked any pathologist about the definition of BAC, you would probably get a statement that it represents an in-situ lung adenocarcinoma, a precursor of invasive carcinoma or something similar. If however, one looked in detail at various lesions which had historically been classified as BAC by pathologists, you would find more entities than you like, including not uncommonly adenocarcinoma with some lepidic growth but also with less than a subtle invasive component.1 Doing away with BAC terminology is a cornerstone of the recent sweeping movement to reclassify the nomenclature of pulmonary adenocarcinoma. This action has been endorsed by some of the leading organizations in pulmonary medicine, including the American Thoracic Society (ATS), European Respiratory Society (ERS) and International Association for the Study of Lung Cancer (IASLC).1 The first author of this truly "state of the art" review published earlier this year, from here on referred to as the Manuscript, is a pathologist, Dr. William Travis of Memorial Sloan Kettering Cancer Center. Those of you who had the privilege of hearing his talks during this year's South Carolina Society of Pathologists (SCSP) meeting, and feel they have a good grip on the recent developments in the domain of lung carcinoma, may tune out or stay tuned in for a bit of a review on this topic. As they say: "Repetition is the mother of learning." My goal here is to provide a brief overview of some of the recent diagnostic and therapeutic developments in the field of lung cancer and to elucidate the key role a pathologist plays in the process, using some of the concepts laid out in the Manuscript.

Some of you are perhaps wondering about the title of this piece and why some of it is in quotes. The quoted part actually is the title of an editorial that appears in the same issue of the Journal of Thoracic Oncology as Dr. Travis's seminal paper.2 This editorial is by MUSC's own esteemed pulmonary physicians, Drs. George Simon and Gerard Silvestri. They applaud Dr. Travis' efforts and success in "thinking like the clinician", for having led the project that eventually resulted in a more clinically relevant classification of lung adenocarcinoma.2 Unquestionable, this era of personalized medicine and continuously emerging targeted cancer therapies which at times supplant traditional chemotherapy, has increased demands on surgical pathologists to vigilantly seek more specific diagnoses when it comes to lung cancer. In other words, it is rarely acceptable anymore to say in your report "non-small cell carcinoma, not otherwise specified (NSCLC, NOS)", not even for small biopsy specimens.

Why? Because the current optimal treatment of lung cancer relies on accurate histopathologic diagnosis, and up to 70% of lung cancer diagnoses nowadays are made based on small biopsies and cytologic specimens and individualized treatment plans are laid out based on the diagnoses from such samples. Advanced stage, unresectable non-small cell lung cancers used to be treated with platinum based chemotherapy as the gold standard. This is no longer the case. Numerous clinical trials in the past several years have shown that several novel oral agents (Gefitinib, Erlotinib, Crizotinib) have similar efficacy and better tolerance when compared to conventional chemotherapy for treatment of advanced stage non-small cell lung cancer. New chemotherapies are also emerging, an example with lung cancer relevance being Pemetrexed. Which one of these is selected for a treatment regimen depends uniquely on the histologic tumor type. Gefitinib and Erlotinib are small molecule EGFR tyrosine kinase receptor inhibitors indicated in EGFR mutated lung adenocarcinomas (up to 30% of adenocarcinomas). Crizotinib earned FDA approval in August of this year, and is indicated in non-small cell cancers positive for ALK gene rearrangements (~5% of adenocarcinomas). Pemetrexed is a folate antimetabolite indicated for use in non-squamous lung cancers. It is ineffective in squamous cancer presumably due to the higher level of thymidilate synthase expressed by cancer cells with squamous lineage. Another quite popular agent is Bevacizumab, a monoclonal antibody targeting VEGF. It is contraindicated in squamous carcinoma due to the risk of potentially fatal pulmonary hemorrhage.

It is clear, then, that histology matters and we pathologists are increasingly expected to take it to the limit in the diagnosis of lung cancer, which is pretty awesome, because it puts us right back in the spotlight! This also means more work and dedication towards optimizing tissue use. Small biopsy or fine needle aspiration materials from a lung lesion, need to be triaged from the get-go in terms of the likelihood of needing ancillary studies, such as immunohistochemistry (IHC) and molecular profiling. IHC is almost a given for most poorly differentiated non-small carcinomas, and a good number of them will also need mutation studies. This means that we should not and cannot use IHC indiscriminately, because it may lead to depletion of precious tissue. It is considered good practice to choose a limited battery of IHC stains based on clues the tumor offers from an H&E or smeared slides in cytology. So for instance, if the main differential is between solid type adenocarcinoma and squamous carcinoma, a good starting point may be thyroid transcription factor (TTF-1; usually positive in adenocarcinoma and negative in squamous carcinoma) and high molecular weight keratin (such as CK5/6; usually positive in squamous carcinoma and negative in adenocarcinoma). If additional morphologic features are present suggesting neuroendocrine (NE) tumor differentiation, one can select an NE marker or two to add to the IHC stain panel.

Our Department's collaboration with MUSC's thoracic oncology clinical colleagues has become ever more critical recently, in part because of the above outlined increasing demands. As of July 1, 2011, we offer in-house testing for the current standard of care lung cancer mutation panel: PCR-based mutation tests for EGFR, KRAS and a FISH test for ALK gene rearrangements. Drs. Julie Woolworth, Daynna Wolff and Rick Nolte have been invaluable in bringing these tests on line; as well as ensuring smooth work-flow and effective communication of results to clinicians. We have also taken part in devising the algorithm for performing the mutation testing sequence which has been accepted by all members of the thoracic oncology tumor board. Taking into account the scientific fact that major tumor mutations tend to be mutually exclusive, we perform the testing sequence in the order deemed most clinically relevant and cost-effective by the group. Each lung cancer case referred to the molecular laboratory for mutation profiling gets tested for EGFR mutation first. If this is positive, we stop there. If negative, we proceed to testing for KRAS mutations (present in up to 30% of cases). If this is positive, we stop, and if negative we finalize the sequence by performing FISH for ALK gene rearrangements. Because PCR-based mutation analysis usually leads to depletion of tumor from paraffin blocks of small biopsies or cytology cell blocks, it is important to remember to cut and store 2 unstained slides in the file prior to beginning the mutation testing sequence, in case ALK FISH needs to be performed.

What does the future bring? It seems that genetic and therapeutic research in thoracic oncology, and especially lung cancer, is the new kid on the block and is here to stay. The recent emergence of histology, at times an underrated factor, as one of the key factors determining optimal patient treatment should be taken as a gift by pathologists hoping to make strides in the arena of lung cancer research. Expect the level of detail needed in your diagnostic report of lung cancer cases to increase steadily and considerably. Envision yourself signing out a report as follows "Adenocarcinoma: solid (50%), acinar (30%) and micropapillary (20%) growth pattern" with an increasing number of gene mutations specified perhaps even separately for each growth pattern that can successfully be micro-dissected from the paraffin block. Because of the prognostic significance of different growth patterns, subtyping lung adenocarcinoma on this basis has become a practice recommendation in the Manuscript.1 Molecular testing of individual growth patterns is still largely in the research phase. However, because lung adenocarcinoma often has more than one growth pattern, it is not unreasonable to expect this level of detail entering the clinical setting. The rapidly accruing knowledge of genetic aberrations in lung cancer and exploitation of that knowledge to create new and improved treatments may turn advanced stage non-small cell lung cancer into a curable disease. Let's remain hopeful.

References:

1. Travis WD, Brambilla E, Noguchi M et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma. J Thorac Oncol 6(2);2011:244-285.

2. Simon GR and Silvestri GA. You Just Can't Call it Lung Cancer Anymore. J Thorac Oncol 6(2);2011:239-240.

SOME INTERESTING FACTS ABOUT MUSC

- MUSC has more than 11,000 employees and is the largest non-federal employer in the Charleston metro area.
- A 2007 study showed that MUSC had greater than $2.3 billion per year in economic impact on the State of South Carolina.

MUSC Clinical Care – Serving the healthcare needs of our citizens

Excellence in clinical care.

- U.S. News & World Report (USN&WR) Best Hospitals rankings for 2011-
  - MUSC is 1st for Charleston metro area hospitals.
  - Our programs in Gastroenterology, Ear/Nose/Throat, and Pediatric Cardiology and Heart Surgery are nationally ranked.
  - Other MUSC "high performing" specialties are Cancer, Cardiology and Heart Surgery, Geriatrics, Gynecology, Nephrology, Neurology and Neurosurgery, Orthopaedics, Psychiatry, Pulmonology, Rheumatology, and Urology.
  - 37 MUSC physicians in 24 specialties are recognized as Top Doctors.
  - MUSC is a leader in ensuring excellent care in Heart Attack, Heart Failure, and Stroke.
- In 2011, performed in the **top 10%** of hospitals nationwide in patient satisfaction and was recognized with the Outstanding Patient Experience Award by Health Grades for this achievement.

Service to the State of South Carolina.

- 700 physician members providing more than 1 million clinic appointments per year.
- 709 hospital beds.
- The only Level I Trauma Center in the region.
- The state's most comprehensive Neonatal Intensive Care Unit.
- The only Transplant Service Line in the state – providing kidney, liver, lung, heart, pancreas, and blood and marrow transplants.
- REACH MUSC provides urgent state-wide consultation by our stroke team at select hospitals in S.C. Supported by the Stroke Center of Economic Excellence/Endowed Chair program, we have already reached over 1,000 patients in S.C. through this initiative.
- Outreach in many other areas including Heart Attack and Perinatal care.
- More than 74,000 emergency room visits per year and over 25,000 surgical cases per year.
- Over 34,000 admissions for a total of more than 211,900 patient days per year.
- More than $147 million of uncompensated care provided to S.C. residents per year.
- Our Hollings Cancer Center is S.C.'s only National Cancer Institute (NCI)-designated cancer center and is one of only 65 such NCI-funded centers in the U.S.

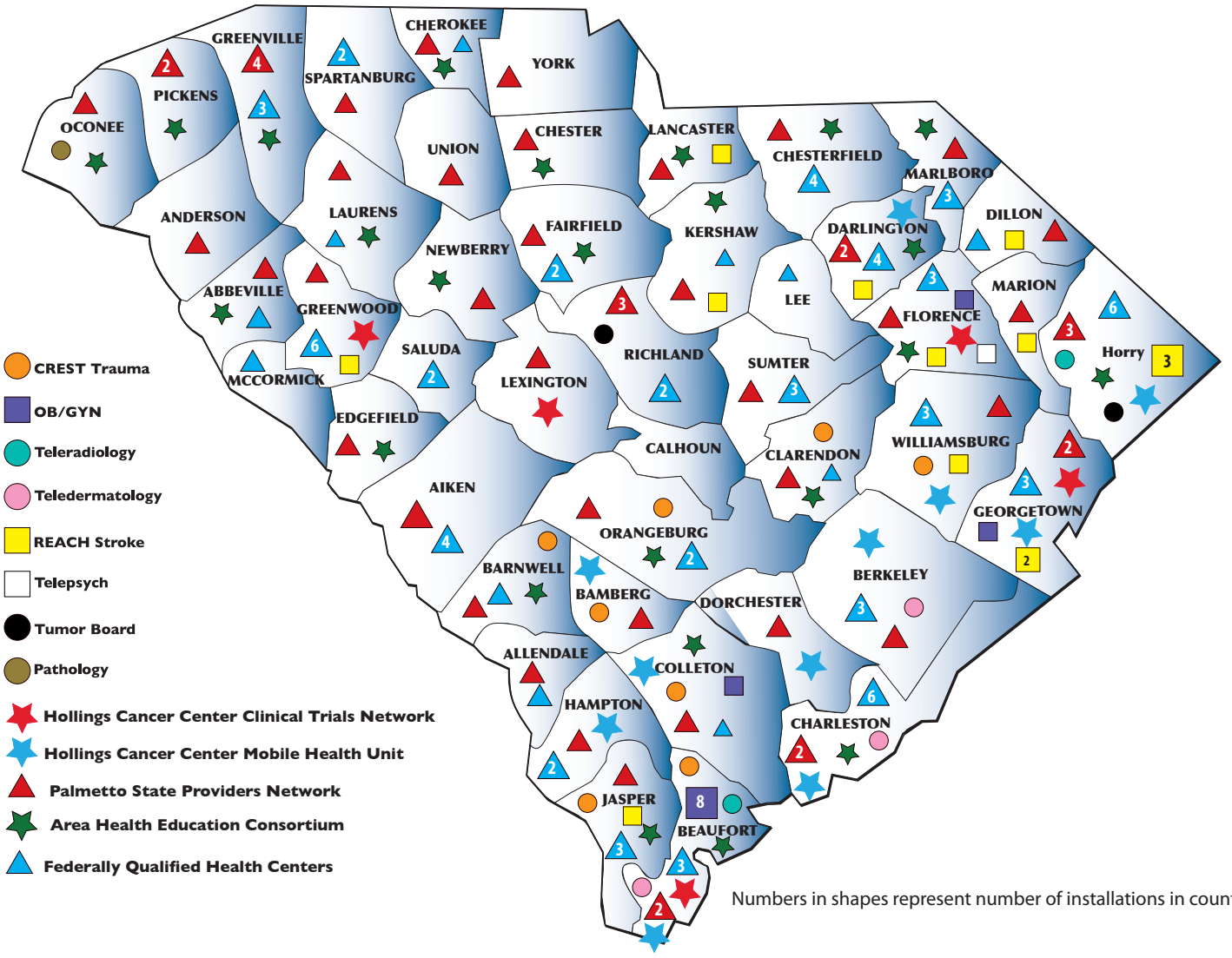
MUSC Education – The oldest and most highly ranked medical school in S.C.

- Recognized as in the top 10 most popular medical schools by U.S. News & World Report.
- Approximately 3,200 applications for our medical school class in 2011 – a 20% increase over 2010.
- 672 medical students.
- 88% of medical students are from S.C.
- In the top half of medical school graduates in the U.S. who practice in the state where they were educated.
- In the top 1/3 of medical school graduates in the U.S. who go into primary care medicine.
- In the top 1/4 for medical school graduates in the U.S. who practice in rural areas.
- In the top 1/10 for medical school graduates in the U.S. who practice in underserved areas.
- 654 residents and fellows are trained at MUSC every year – more than any other S.C. hospital.

MUSC Research – Solving the problems of tomorrow's patients

- $214.6 million in total research funding for the College of Medicine, a 5.1% increase over the prior year.
- Rank 47 of medical schools in National Institutes of Health (NIH) funding.
- During the past 4 years, College of Medicine faculty have made-
  - 151 records of invention;
  - 48 patent applications; and
  - 5 patents have been issued.
- 127 PhD and 57 MD/PhD graduate students.
- 185 post-doctoral students.
- Home to the S.C. Clinical and Translational Institute – one of only 60 such NIH-funded centers in the U.S.

Telemedicine, Palmetto State Providers Network, and other Outreach Activities



Numbers in shapes represent number of installations in county

THE 5/5 PLAN

Nancy Reilly Dixon

Through collaboration with physician leaders, faculty, service line administrators and staff, the laboratory management team is looking at ways to use limited resources more wisely. 5/5 IMPROVE projects have been identified that will offer the same level of quality service Laboratory Services has always provided, but with more efficiency and less waste. Some examples of cost containment projects underway are: improved blood product utilization, daily lab test utilization, staff overtime reduction, supply/reagent cost negotiations, blood culture contamination reduction and referral testing cost containment. So far $2.39 million dollars in potential savings have been identified. The long term goal is to prepare for expected cuts in Medicaid funding. To this end Laboratory Services is working to decrease laboratory cost per adjusted patient discharge from $917 to $871 by June 2012.

101st USCAP ANNUAL MEETING

March 17-23, 2012
Vancouver Convention Center
Vancouver, BC, Canada
www.uscap.org/newindex.htm?101st/index.htm

UNITED STATES & CANADIAN ACADEMY OF PATHOLOGY
LEADING PATHOLOGY EDUCATIONAL EXCELLENCE

Pratt-Thomas Symposium in Surgical Pathology

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

John R Goldblum, MD
Cleveland, Ohio

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

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

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

Anthony Montag, MD
Pritzker School of Medicine, The University of Chicago, Chicago, IL

Marisa Nucci, MD
Assistant Professor, Pathology, Brigham and Women's Hospital, Boston, MA

Victor E. Reuter, MD
Memorial Sloan-Kettering Cancer Center's Pathology Core Facility, New York, NY

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

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

McKee Cytology Seminar

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

Michael R Henry, MD
Mayo Clinic, Rochester, MN

Martha B Pitman, MD
Massachusetts General Hospital, Boston, MA

Stephen S. Raab, MD
Memorial University Hospital of Newfoundland

Eva M. Wojcik, MD
Loyola University Medical Center, Maywood, Il

Gadsden-Holbrook Symposium in Clinical Pathology

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

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

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

Jan A. Nowak, MD PhD
Northshore University Health System

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

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

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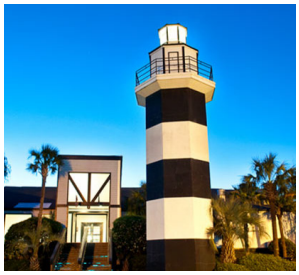
MUSC DEPARTMENT *of* PATHOLOGY & LABORATORY MEDICINE

HOLIDAY PARTY 2011

The annual departmental Holiday Party was held at the Lighthouse on the Creek and was one of the livliest in recent memory.

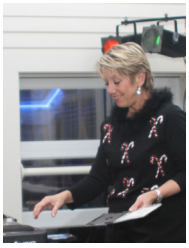


Individuals and groups lined up to have their annual portrait made by Jim Nicholson and Graylin Nelson.

Several couples claimed this was their fourteenth year for a picture.

Teresa Kennedy and other volunteer freelance photographers made sure the party was well documented.

The caterers kept the great food coming.



The DJ kept the music flowing.

And the the dance floor stayed well filled ...

with lively action.

While others enjoyed quieter moments in the company of their friends.