PATHOLOGY & LABORATORY MEDICINE

NEWSLETTER

Volume 3, Issue 4 2012

Holiday Greetings and the Very Best Wishes for the New Year!

Inside this issue:

CONGRATULATIONS!

PROMOTION

Nicholas I. Batalis, M.D.

To Associate Professor

Effective January 1, 2013

GOLDEN APPLE AWARDS

December, 2012

First Year Class (Nominees)
Dr. Mike Caplan
Dr. Debra Hazen-Martin

Second Year Class (Nominees)
Dr. Nick Batalis
Dr. Mike Caplan
Dr. Erin Presnell
Dr. Sally Self
Dr. Jerry Squires
Dr. Daynna Wolff

Special Appreciation
Dr. Debra Hazen-Martin (Winner)

Ellen C. Riemer, M.D., J.D.,

had two abstracts presented recently at the annual meeting of the **American Academy of Chest Physicians** (AACP) which took place in Atlanta in October 2012.

The first abstract (below) received the award for "Outstanding Case Presentation."

"Organizing Pneumonia and Positive anti-CCP as Initial Presentation of Rheumatoid Arthritis" *(received award for "Outstanding Case Presentation")*

and

"Pulmonary Capillaritis and Diffuse Pulmonary Hemorrhage in a Patient with Moderately Positive Anti-PL 12 Antibodies"

CONGRATULATIONS!

TO:
Dr. Hainan Lang
and
Jim Nicholson
on winning a
Nikon Image of Distinction Award
in the
2012 Photomicrography
Competition!

http://www.nikonsmallworld.com/galleries/entry/2012-photomicrography-competition/84

FACULTY EXCELLENCE AWARDS

Nicholas Batalis, M.D.
Michael Caplan, M.D.
Janice M. Lage, M.D.
John S. Metcalf, M.D.
Frederick S. Nolte, Ph.D., D(ABMM), F(AAM)
Jonathan S. Ralston, M.D.
Sally E. Self, M.D.
Jerry E. Squires, M.D., Ph.D.
Lisa L. Steed, Ph.D.

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.**

The faculty nominated above teach the 1st & 2nd year students. We are in the process of receiving the complete list for the teacher nominations for the 3rd & 4th year students. Once this complete list is received, it will be emailed and also put in the next newsletter.

Perry V. Halushka MUSC 2012 Research Day Winner List

Category	Place	Winner	Lab
PostDoc/Resident/Fellow I Poster	1st	Yazhi Xing	Dr. Lang's Lab
PostDoc/Resident/Fellow II Poster	1st	Ying Xiong	Dr. LaRue's Lab
PhD V Oral	1st	Lindsay T. McDonald	Dr. LaRue's Lab
VA – Oral	1st	Lindsay T. McDonald	Dr. LaRue's Lab
VA – Poster	1st	Dayvia Laws	Dr. LaRue's Lab
Health Disparities – Poster	2nd	Dion Foster	Dr. Turner's Lab

ARRIVALS & DEPARTURES

New Hires:

Yu Han
Visiting Scholar
Dr. Sha's lab
October 15, 2012

Christopher Duckworth
Research Specialist 1
Dr. Cheung's lab
October 15, 2012

Lu Wang
Volunteer
Dr. Wang's lab
October 24, 2012

Debra Ellisor
Research Specialist II
Dr. Spyropoulos's lab
November 15, 2012

Departures & Transfers:

Melissa Scheiber
Graduate Assistant
Dr. Watson's lab
December 14, 2012

It's a BOY!

Congratulations to Dr. Nicole Miller, our Hematopathology Fellow, on the birth of her son. Hudson Teague was born on December 10, 2012 at 1:04 pm and weighed 9 pounds 3 ounces. Hudson's brothers, Keegan and Grant were excited to welcome him to the family.

102ND USCAP ANNUAL MEETING
MARCH 2-8, 2013, BALTIMORE, MD

PATHOLOGY SPRING SYMPOSIA
APRIL 22-27, 2013 AT KIAWAH

APC 2013 ANNUAL MEETING
JULY 10-12, 2013, BOSTON, MA

CAP 2013
THE PATHOLOGISTS MEETING
OCTOBER 13–16, 2013, ORLANDO, FL

9 Tips for Safer Computing

1. **Install OS and 3rd party patches**
   It is critical to keep your software up-to-date. Newest versions contain fixes for discovered vulnerabilities. Enable automatic update feature in OS and application software.
   Windows – Control Panel
   Mac OSX – System Preferences

2. **Use current antivirus, antispyware and firewall software Anti-virus software**
   "Used to identify and remove computer viruses, as well as many other types of harmful computer software, collectively referred to as malware" Wikipedia
   offers ongoing protection, daily scans, daily updates

Anti-spyware software

- Protects your computer from malicious spyware.
- Spyware may monitor your online activities and collect personal information while you surf the web.
- Periodically scans your computer for spyware.

Firewall Software

- Firewall software and/or hardware monitors the communications between your computer and the outside world (the Internet). Firewalls prevent unauthorized access to or from a private "network" (i.e., your home computer). You can implement a firewall in either hardware or software form, or a combination of both.

At Home – install Internet Security Packages

- Some commercial internet security packages include anti-virus, anti-software and firewall software. Norton, Trend Micro, McAfee, EEye, ESET, AVG are a few vendors you can explore.
- To be effective virus definitions **must** be updated routinely.

3. **Use strong, complex passwords**
   - At least one alphabetic, one numeric and one special character
   - At least 7 characters long
   - Mixed case
   - Not similar to other passwords or your name
   - Not found in the dictionary
   - Choose a password that is difficult to guess
   - Protect your password and do not share it

4. Lock your computer

- Lock your computer or handheld device while unattended and use a screen saver that is password protected.
- Windows XP Professional and Windows Vista, press **Ctrl+Alt+Delete**, and then click **Lock Computer**.

5. Backup Data at Home

- Be prepared for the worst by backing up critical data and keeping backups in a separate, secure location.
- Use supplemental hard drives, CDs/DVDs or flash drives.
- Backup data, files, music, videos, and pictures.

6. Be aware of email security Phishing

- Greet emails seeking personal information with skepticism.
- Be leery of alarming statements that urge you to respond immediately.
- Do not reply to phishing emails.
- Do not click on links in emails.

Spam

- Spam is anonymous, unsolicited junk email sent indiscriminately to huge numbers of recipients.
- Do not open email that is obviously spam.
- If you do open spam, do not click on any links.

Attachments

- Computer viruses and other malicious software are often spread through email attachments.
- If a file attached to an email contains a virus, it is often launched when you open (or doubleclick) the attachment.
- Don't open unexpected email attachments.

Links

- Approach links in an email with caution. They might look genuine, but they could be forged.
- Copy and paste the link to your web browser.
- Type in the address yourself.
- Or even Google the company and go to their website from the search results.

7. Don't install unknown or unsolicited programs on your computer

- Cute games, utilities and other fun stuff are often used to disguise spyware/malware

Spyware

- Software hidden inside more harmless software that at its most benign records information such as web sites visited or at its worse can do keystroke logging in order to steal your information.

Malware

- *Malicious software* designed to infiltrate or damage a computer without the owners awareness or consent

8. Protect your private information

- Do not send sensitive personal information through email unencrypted.
- Make sure any web site that requests personal information uses SSL to encrypt your data
- Look for https and lock displayed on web browser
- Watch out for Phishing emails that ask for personal or financial information

9. Maintain physical security of your computer

- Be aware of your surroundings
- Do not leave phones, laptops, handheld devices etc. unattended
- Lock your office when you leave
- Do not allow others to use your computer

You are cordially invited to

the twenty-sixth annual

Charity Ball

Saturday, February 16, 2013
7pm until 11pm
silent auction begins at 7pm
Memminger Auditorium
Tickets $50 per person
Alumni may purchase 2 tickets for $45 each
Each additional ticket is $50

For more information: http://academicdepartments.musc.edu/com/stu_affairs/events_activ/charityball/index.html

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

To: All MUSC and MUSCP/CFC Faculty, Staff, Residents, Fellows and Volunteers

From: Mark Sothmann, PhD, Vice President for Academic Affairs and Provost
Patrick J. Cawley, MD, Executive Medical Director
Harry Clarke, MD, Associate Dean for Graduate Medical Education and President of the Medical Staff
Howard Evert, MD, President and Director, Carolina Family Care
Steve Valerio, CEO MUSC Physicians and Associate Dean of Finance, College of Medicine

Date: December 1, 2012

Re: Annual CATTS or Mandatory Training Requirements and Deadline – June 30, 2013

It is the policy of the Medical University of South Carolina, MUSC Physicians, the Medical University Hospital Authority and our affiliates to comply with the law and to follow ethical business practices. To promote understanding of various federal and state laws, key policies and regulations, we jointly require that all employees and affiliates complete annual CATTS or Mandatory training.

A workgroup comprised of representatives from MUSC, MUSCP/CFC and MUHA (human resources, compliance, risk management), the medical staff office, and OCIO has collaborated to establish a single annual deadline and common process for communicating with our combined faculty, staff, trainees, and volunteers regarding annual training requirements and deadlines. It is our intent to lessen confusion regarding which individuals are required to complete which sets of training, as requirements can vary depending upon employment status, medical staff membership, position responsibilities and trainee/student status. Since a significant portion of our combined population falls into more than one of these categories, the requirements can become even more confusing.

As we enact this unified schedule, a single **deadline of June 30, 2013** has been set for the current fiscal year and lessons have begun to be assigned within the system.

The attached grid outlines in very general terms the expectations of each group; however, the best source of information regarding which training is required for a specific individual is the CATTS online training system. Individuals can access the system easily at www.musc.edu/catts and log in using their NetID and password. All lessons for the June 30, 2013 deadline will be loaded by April 1, 2013 and individuals should complete all lessons by the assigned deadline shown within the system.

It is very important that everyone complete the annual mandatory training process. Failure to complete the assigned training by the stated deadline may result in disciplinary action as specified in human resources policies, the faculty handbook, and the graduate medical education handbook as applicable.

Thank you for your cooperation. Please address any questions regarding this process to your supervisor or your respective Human Resources office.

"An equal opportunity employer, promoting workplace diversity"

Employment Category	Assignments Required by Entity			
	University (MUSC)	**Hospital (MUHA)**	**Practice Plan (MUSCP/CFC)**	**Housestaff (GME)**
Clinical Faculty	3 OSHA lessons, HIPAA, and Harassment	Lessons as assigned by an individual's specific role(s) and responsibilities within a clinical setting. These may include, but are not limited to: • Safety Initiatives • Restraints • Health Information Services • Anticoagulation and Blood Products • Sharp Penetration Injuries • Pain Assessment and Management • Insulin Drip Calculator • Drug Disposal	3 OSHA lessons, HIPAA, and Harassment	n/a
Non-Clinical Faculty	3 OSHA lessons, HIPAA, and Harassment	n/a	3 OSHA lessons, HIPAA, and Harassment	n/a
University Staff	3 OSHA lessons, HIPAA, and Harassment	Lessons as assigned by an individual's specific role(s) and responsibilities within a clinical setting.	n/a	n/a
MUSCP (UMA) Staff	3 OSHA lessons, HIPAA, and Harassment	Lessons as assigned by an individual's specific role(s) and responsibilities within a clinical setting.	3 OSHA lessons, HIPAA, and Harassment	n/a
MUSC & MUSCP Credentialed Staff (PA's, NP's, etc.)	3 OSHA lessons, HIPAA, and Harassment	Lessons as assigned by an individual's specific role(s) and responsibilities within a clinical setting. These may include, but are not limited to: • Safety Initiatives • Restraints • Health Information Services • Anticoagulation and Blood Products • Sharp Penetration Injuries • Pain Assessment and Management • Insulin Drip Calculator • Drug Disposal	3 OSHA lessons, HIPAA, and Harassment	n/a
Current Residents and Fellows (Requirements for <u>new</u> Residents and Fellows are different)	3 OSHA lessons, HIPAA, and Harassment Residents as Teachers LCME – Medical Student Longitudinal Objectives	Lessons as assigned by an individual's specific role(s) and responsibilities within a clinical setting. These may include, but are not limited to: • Safety Initiatives • Restraints • Health Information Services • Anticoagulation and Blood Products • Sharp Penetration Injuries • Pain Assessment and Management • Insulin Drip Calculator • Drug Disposal	n/a	n/a
Non-hospital staff working in a clinical setting	3 OSHA lessons, HIPAA, and Harassment	Lessons as assigned by an individual's specific role(s) and responsibilities within a clinical setting.	3 OSHA lessons, HIPAA, and Harassment	n/a

1. Employees with a dual employment status or who are also students/trainees may have additional lessons required.
2. This grid serves as a guideline ONLY. Employees/trainees are required to complete <u>ALL</u> lessons appearing in their individual list by the date indicated within the CATTS system.

I CAN'T FIT INTO MY GENES

Demetri Spyropoulos, Ph.D.
Associate Professor, Research

More is known about the scientific basis of good health than ever before, as evidenced by the steady increases in health and longevity over the past century. These gains have been the result of the prevention and treatment of infectious diseases, improved nutrition, and better lifestyle choices such as reduced tobacco use. These impressive and hard-won gains are now threatened by an obesity epidemic [1].

In the Spyropoulos lab, we study the genes that control the body plan: what goes where and in what amounts, giving each of us our own distinctive appearance, abilities and mannerisms. On the cellular level, our genes control the process of differentiation that defines the identity and numbers of various cell types such as neuron, muscle or fat cells, which in turn pattern the individual. Although these processes continue throughout life, a great many occur in the fetus where the lion's share of cells' fates are determined. How is this important to health and longevity and what role does it play in the obesity epidemic?

Conventional wisdom is that family history is a prime determinant of health and longevity, but what 'family history' encompasses is unclear. Many presume that genetics supersedes lifestyle/environment. "The father of modern genetics" Gregory Mendel developed genetic laws of inheritance, working with pea plants in the late 1850's. These laws state that one fixed 'factor' (a gene) from each parent combine to control specific dominant/recessive traits in an offspring. However, studies on identical twins show that among genetics and lifestyle, that lifestyle can account for 70-80% of an individual's health [2]. The recent field of 'epigenetics' is the study of heritable changes in gene activity (i.e. which genes are 'off' or 'on') without changes or differences in the gene's DNA sequence. A growing body of epigenetic evidence indicates that the environment can change an individual's traits, carried not just from one cell division to the next, but from parent to offspring [3]. Thus, 'family history' can be considered a combination = gene X environment (individual) X environment (ancestral). This is a curious turn of events in science, since the proposed inheritance of acquired traits via environmental forces, or "soft inheritance" had been unequivocally rejected from before Mendel's time until recently [3]. J. B. Lamarck, who is known for his "use/disuse" theory of evolution, proposed this in the early 1800's. So, "soft inheritance" must now be reconsidered, at least in part, since environmental exposures can shift not only traits within a lifetime but across generations!

Since the majority of cells' fates are determined in the fetus, it is likely to be exquisitely sensitive to environmental exposures that change gene activities, especially those that control the body plan. Although assessed throughout life, early errors in the body plan and cell identities 'set the trajectory' for life-long and trans-generational health. Endocrine disruptors are a major category of environmental pollutants that interfere with the body's hormonal system [4]. Many groups, including ours, have shown that they also interfere with the activities of genes that control the body plan [5]. Some endocrine disruptors, referred to as obesogens, are likely contributors to the obesity epidemic [6]. Studies performed in model organisms, including the mouse, have produced a fundamental understanding of this process. But how does one bridge the gap to humans and protected or endangered species?

The process of differentiation, determining a cell's fate to become a muscle or fat cell for example, starts with cells that can become many cell types, referred to as undifferentiated 'stem' cells. Modern stem cell technology allows us to take a differentiated adult cell (e.g. skin fibroblast) and de-differentiate it to a stem cell. This technology offers 'test tube' (*in vitro*) surrogates for fetal exposure studies, with the added benefit that cells can be used to assess pollutant exposures, including dosage, timing and mixtures in a higher throughput manner than using organisms [7, 8]. Some of the body-plan genes that we study pattern reproductive organs & control fertility, while others pattern thoracic structures, such as the lung and mammary gland. Our lab's work on the lung is done in conjunction with the Baatz lab. Our joint efforts on lung cryopreservation led us to establish stem cells from a Pygmy Sperm Whale, a deep diving mammal, stranded on Myrtle Beach [9].

For comparative studies, the lab has also established stem cells from: mouse embryos, pigs that are a terrestrial relative of the whale, American alligators (with the Guillette and Kohno labs), and adult-derived human stem cells obtained from colleagues at Harvard. Our early findings suggest that even after de-differentiation, the 'reprogrammed' adult-derived cells still 'remember' their history when induced to make fat cells. For example, only the deep diving whale cells know what to do under extreme conditions and the cells from an alligator living in a contaminated site appear to remember or possibly even 'need' contaminants to thrive.

Our team of investigators is examining fat cell differentiation (adipogenesis) as part of a joint effort to study the impacts of environmental & anthropogenic pollutants from the Gulf oil disaster. The Gulf of Mexico Research Initiative (GoMRI) is a 10-year independent research program, established through a $500 million financial commitment from BP to investigate effects of the *Deepwater Horizon* incident. GoMRI is funding our study to identify obesogens in both crude oil and the 'detergents' used to disperse the oil. The larger mission of the GoMRI is to improve society's ability to understand and mitigate the impacts of hydrocarbon pollution and stressors on the marine environment and public health. If we know which molecules are the most harmful, we can selectively target our efforts at breaking them down.

"All that you touch
All that you see
All that you taste
All you feel…"

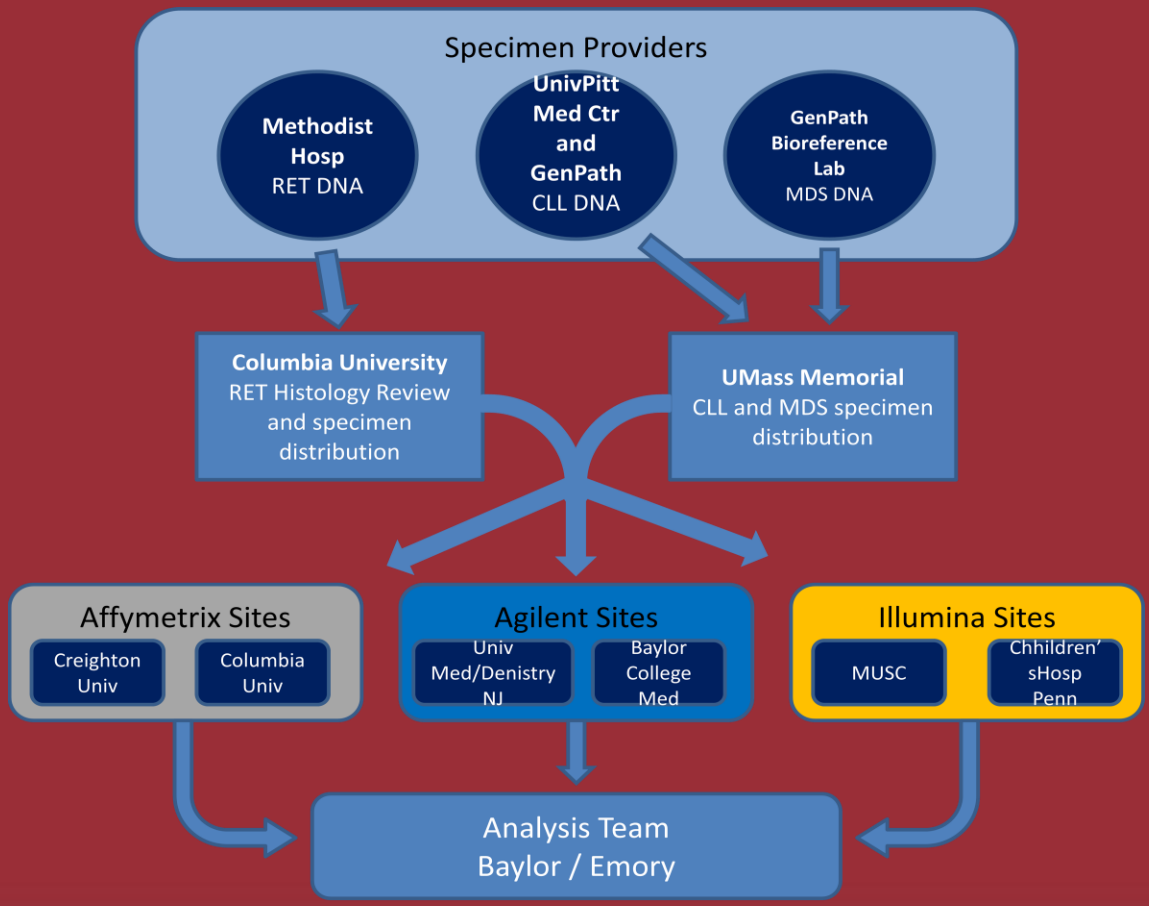
From "Eclipse" (Roger Waters; Pink Floyd)

1. Stewart, S.T., D.M. Cutler, and A.B. Rosen, *Forecasting the effects of obesity and smoking on U.S. life expectancy.* N Engl J Med, 2009. **361**(23): p. 2252-60.
2. v, B.H.J., I. Iachine, A. Skytthe, J.W. Vaupel, M. McGue, M. Koskenvuo, J. Kaprio, N.L. Pedersen, and K. Christensen, *Genetic influence on human lifespan and longevity.* Hum Genet, 2006. **119**(3): p. 312-21.
3. Richards, E.J., *Inherited epigenetic variation--revisiting soft inheritance.* Nat Rev Genet, 2006. **7**(5): p. 395-401.
4. Guillette, L.J., Jr. and T. Iguchi, *Ecology. Life in a contaminated world.* Science, 2012. **337**(6102): p. 1614-5.
5. Friedmann, Y., C.A. Daniel, P. Strickland, and C.W. Daniel, *Hox genes in normal and neoplastic mouse mammary gland.* Cancer Res, 1994. **54**(22): p. 5981-5.
6. Janesick, A. and B. Blumberg, *Minireview: PPARgamma as the target of obesogens.* J Steroid Biochem Mol Biol, 2011. **127**(1-2): p. 4-8.
7. Takahashi, K. and S. Yamanaka, *Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.* Cell, 2006. **126**(4): p. 663-76.
8. Reik, W., *Stability and flexibility of epigenetic gene regulation in mammalian development.* Nature, 2007. **447**(7143): p. 425-32.
9. Mancia, A., D.D. Spyropoulos, W.E. McFee, D.A. Newton, and J.E. Baatz, *Cryopreservation and in vitro culture of primary cell types from lung tissue of a stranded pygmy sperm whale (Kogia breviceps).* Comp Biochem Physiol C Toxicol Pharmacol, 2011.

MUSC Cytogenetics Laboratory Participates in a Multi-Laboratory, Cross-Platform Assessment of Cancer Cytogenomic Microarrays for Clinical Oncology Testing

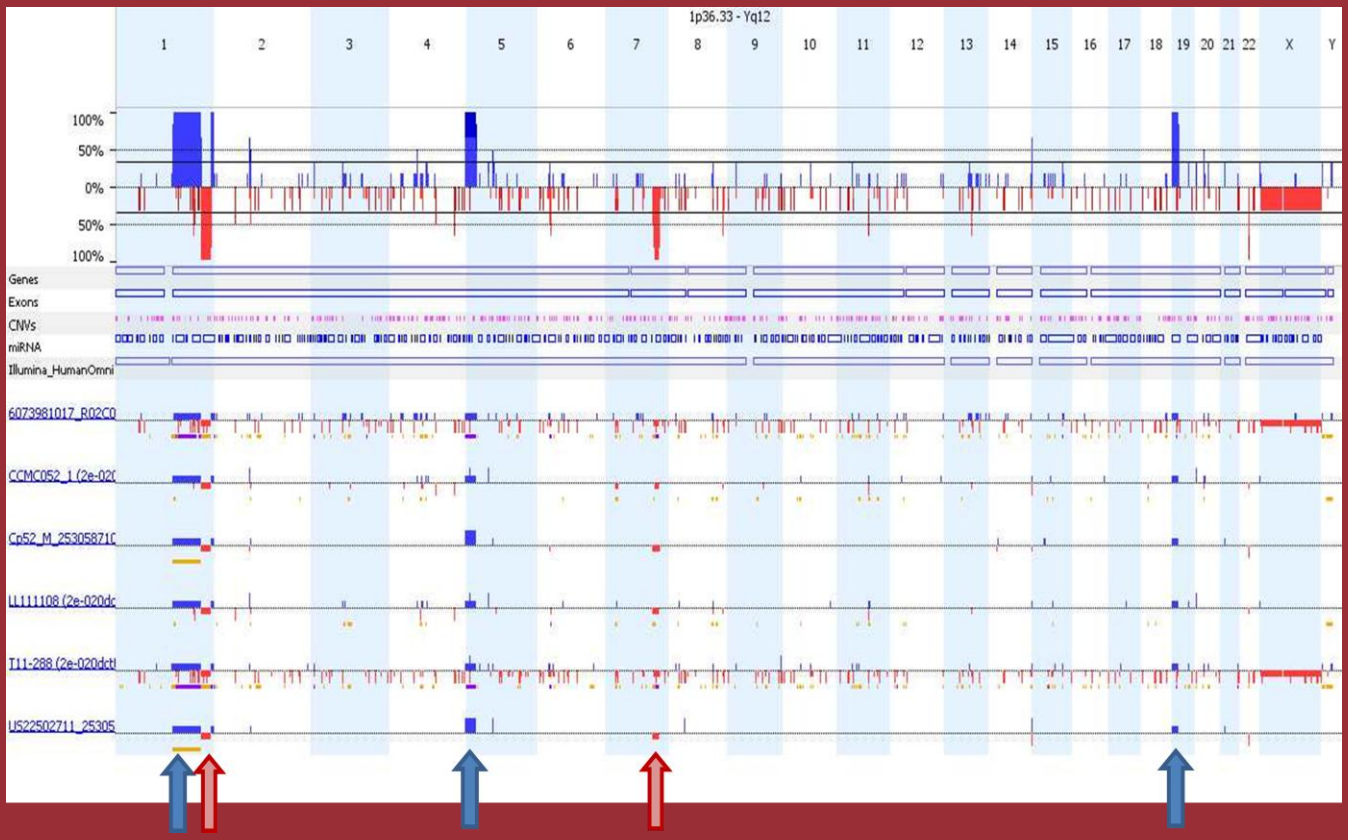
Daynna J. Wolff, Ph.D.
Professor
Laboratory Medicine
Director of Cytogenetics and Molecular Pathology

The MUSC Cytogenetics laboratory was chosen as one of six laboratories to participate in a Cancer Cytogenomics Microarray Consortium (CCMC)-sponsored study to evaluate the clinical utility of cancer cytogenomic microarrays for clinical oncology. The specific aims of the study were to compare the performance of cytogenomic microarrays to the gold standard assays and to assess the cross-platform reproducibility of the commercially available microarrays. For this study, 29 peripheral blood samples from patients with chronic lymphocytic leukemia (CLL), 34 bone marrow samples from patients with myelodysplastic syndromes (MDS) and 30 renal epithelial tumor samples (RET) were provided by The Methodist Hospital, The University of Pittsburgh Medical Center and GenPath Bioreference laboratories. Investigators from Columbia University and the University of Massachusetts Memorial Hospital reviewed gold standard data for each specimen and specimens meeting study criteria were distributed to the six testing laboratories that utilized microarrays from Affymetrix, Agilent and Illumina (two laboratories per each platform).



The participating laboratories, all pioneers in using microarray technology for cancer, were chosen based on their experience and proficiency with one of the array platforms. The project's principle investigators included, Daynna Wolff, PhD, from MUSC, Jackie Biegel, PhD (CHOP), Brynn Levy, PhD (Columbia Univ), Gokre Toruner, MD, PhD (UMDNJ), Marilyn Li, MD (Baylor) and Jill Hagenkord, MD (formerly of Creighton Univ). Each laboratory processed the samples on the platform in use for clinical testing and microarray results were (1) compared to gold standard clinical results, (2) assessed for intralaboratory reproducibility on duplicate samples, and (3) used to determine intralaboratory reproducibility between laboratories using the same microarray methodology. Each laboratory's raw data was provided to Federico Monzon (Baylor) and Michael Rossi (Emory) for the final centralized review. A manuscript describing the study is in preparation and will be submitted to Cancer Genetics in early 2013.

Preliminary results reveal that the microarrays provide high quality clinical information with >90% concordance between "gold standard" and microarray results. For CLL, microarray results were compared to clinical FISH results for probes testing loci at 11q23, 12 centromere, 13q14 and 17p12 and a 95% correlation was observed. A couple of low level FISH-detected abnormalities were not called by laboratories due to the aberration not being above the laboratory-established cut-off rate on the microarray. However, all of the aberrations were detected on the final centralized review. Several abnormal cases were missed by FISH because the probes did not cover the microarray-detected aberrations. For example, in the figure below, each laboratory detected a complex karyotype with gains (shown in blue) and losses (shown in red) for chromosomes 1, 5, 7 and 19 on the microarray, but FISH was reported as normal.



High concordance rates between microarray and gold standard results for MDS (91%) and for the renal epithelial tumors (90%) were also observed. These results suggest that the use of microarrays for clinical diagnosis/prognosis in cancer can augment, or in some places, replace the current gold standard assays.

The microarray cross-platform study is the first sponsored study for the CCMC and the group hopes to fund clinical studies of next generation sequencing for cancer in the future. The CCMC, originally formed in 2008 by a handful of laboratories using microarrays for cancer studies, now boasts over 150 members from the US and abroad. Dr Wolff (MUSC), a founding member, was appointed to the first Board of Directors of CCMC and acts as the Treasurer of the organization. More information on the organization can be found at www.cancergenomics.org .

26S Protesome inhibitor (Bortezomib), Novel role in treating combined antibody/cell mediated rejection

Omar Moussa, Ph.D.
Associate Professor
Laboratory Medicine / Research
Director of HLA Laboratory

The Human Leukocyte Antigens (HLA) are a group of proteins encoded by a series of genes that are located at the short arm of chromosome 6. The HLA system is critical in the immune recognition of self and non-self and the immune response. Antibodies to the HLA epitopes are formed in response to exposure to non-self HLA epitopes after blood/products transfusion, transplanted tissue or pregnancy. Patients with HLA antibodies in their circulation are often referred to as sensitized. The sensitization score is measured by an index named "Panel Reactive Antibodies (PRA).

PRA values have historically been determined by adding patient serum to a panel of HLA typed T lymphocytes. The percentage of cell death is then determined and a value assigned. For example, if 80/100 panel cells reacted in this assay, the PRA value would be 80%. It is important to realize that panel composition could skew PRA results. For example, if every target cell expressed HLA-A*02 and the patient had only one antibody but it was directed against HLA- A*02, the PRA value would be 100%. This is completely misleading data. Another major limitation of reporting PRA values as above is that antibodies to HLA class II antigens could not be assessed.

The implementation of solid phase antibody detection assays using targets expressing a single HLA antigens has permitted accurate assessment of both class I and class II antibodies in recipient sera. The antigens to which these antibodies are directed are considered "unacceptable" donor antigens for these patients. The frequency of those "unacceptable" antigens in the donor population will determine the estimate of the PRA value. In fact, the United Network of Organ Sharing (UNOS) has developed a database containing the HLA antigen frequencies for >12,000 donors. Unacceptable class I and/or class II antigens can be selected and an on-line tool can be used to calculate PRA values (cPRA).

The presence of HLA antibodies in the circulation of patients awaiting transplantation could be a major limitation for access to transplantation. In addition, HLA antibodies are a risk factor for solid organ allograft antibody mediated rejection (AMR). Treatment and management of patients with AMR is challenging task. Common treatment protocols are the use of plasmapheresis and the use of intravenous immunoglobulin (IVIG). Recently, novel treatment protocols involved the use of a plasma cell targeting drug Bortezomib (commonly known as Velcade).

Bortezomib (PS-341) is a selective 26S proteasome inhibitor and has been used to treat antibody mediated rejection (AMR) and in desensitization regimens among allograft recipients. Bortezomib treatment of AMR has been reported to be efficacious in patients with pure AMR as well as in patients with mixed features of T cell mediated rejection (TCMR) and AMR. While the effect of Borezomib on HLA-donor specific antibodies is largely attributed to its effects on plasma cells (PCs), the 26S proteasome is distributed in cells other than plasma cells. Bortezomib's efficacy in mixed ACR/AMR raises the possibility that additional signaling pathways may be impacted when Bortezomib is used. In the current study we used a PBMNC model to investigate whether other signaling pathways are altered. Human peripheral blood mononuclear cells were isolated from normal healthy volunteers and treated with Bortezomib or vehicle control. cDNA microarray hybridization using a 42K gene slide array (Stanford University) was performed on RNA isolated from treated cells. Array normalization and analysis were performed using TIGR software. Pathways were analyzed using Onto-Express. Microarray results were validated with Real-Time PCR.

In Bortezomib treated PBMNC, alteration in T cell activation and signaling pathways were observed in addition to pathways involving B cell signaling. Specifically, an mRNA level of Plexin A2, Plexin-A subset of the semaphorin co-receptor family, was increased 5 fold. Interestingly, Plexin A2 is a key negative regulator of T cell activity, cell proliferation, chemotaxis, differentiation, and cytokine production. Additionally, Tenascin C (a positive regulator of IL 17) expression was decreased with Bortezomib treatment.

Our findings point to significant effects of Bortezomib on T cell signaling pathways. It is tempting to speculate that our observations explain the efficacy of Bortezomib in patients with mixed TCMR and AMR despite variable effects on alloantibody levels. Further studies are needed to document the novel pathways impacted by Bortezomib which may identify potential targets of therapeutic intervention for patients with AMR and mixed ACR/AMR.


Pathology and
Laboratory Medicine
2012
Holiday Party