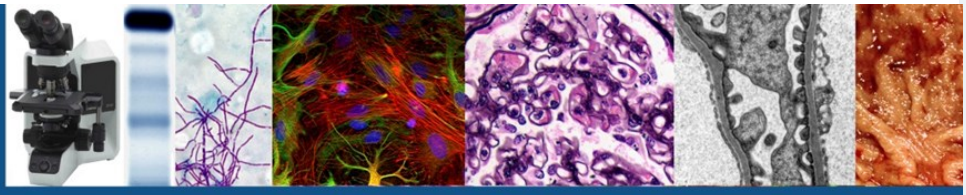
THE PATH WAY

June, 2014 **Volume 5, Issue 2**

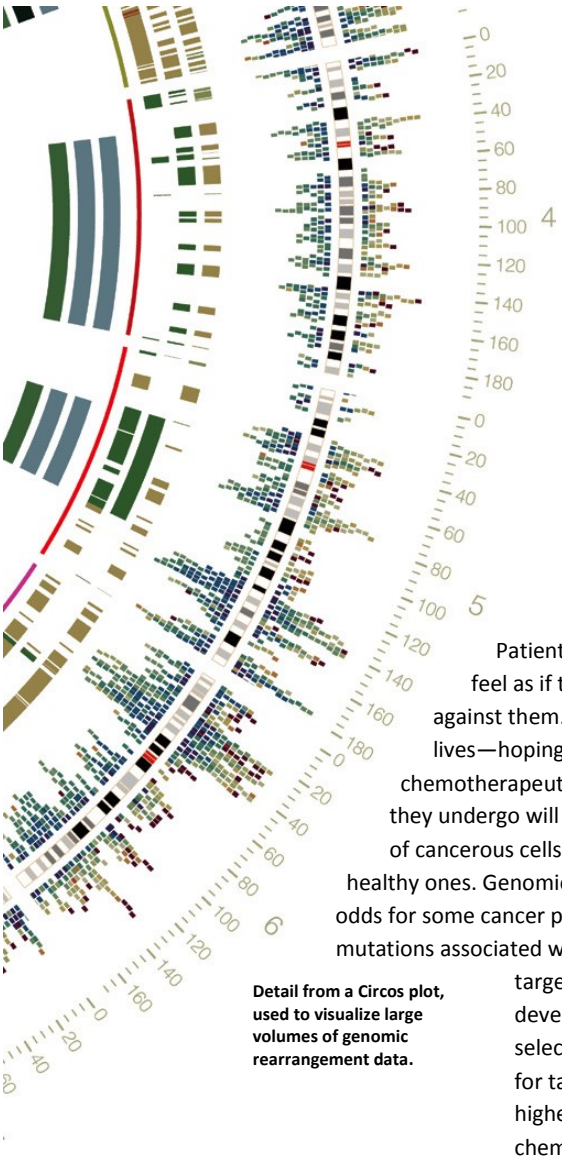
MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA



DEPARTMENT of PATHOLOGY & LABORATORY MEDICINE

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

Inside this issue:



Detail from a Circos plot, used to visualize large volumes of genomic rearrangement data.

Right On Target

Clinical Genomics Identifies Cancer Patients Likely to Benefit From Available Targeted Therapies

BY KIMBERLY MCGHEE

ILLUSTRATION BY MARTIN KRZYWINSKI

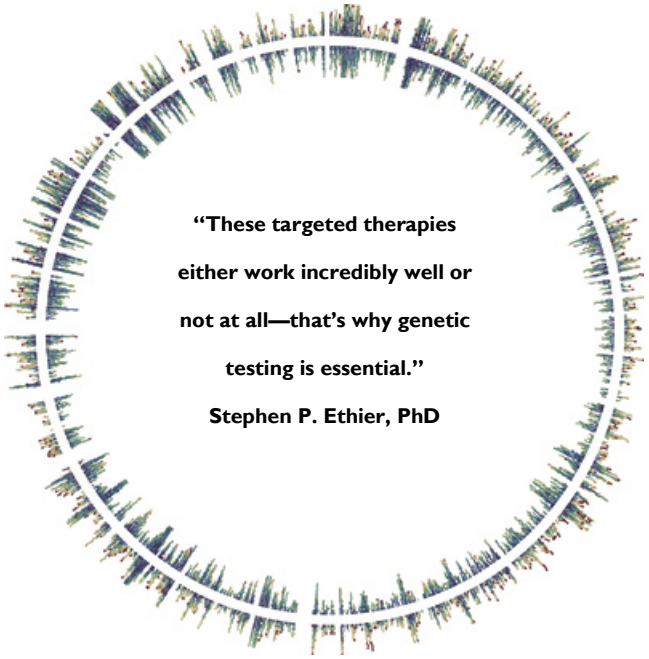
Patients diagnosed with cancer may feel as if the odds have been stacked against them. They are in the fight of their lives—hoping that the sometimes harsh chemotherapeutic or radiation treatments that they undergo will prevent the rapid proliferation of cancerous cells without damaging too many healthy ones. Genomics screening can improve the odds for some cancer patients, potentially identifying mutations associated with cancer subtypes for which targeted therapies exist or are in development. In appropriately selected patients, response rates for targeted therapies are often higher than for conventional chemotherapy.

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).

In January 2014, a new clinical genomics laboratory opened at MUSC under the leadership of **Daynna Wolff, PhD**, Director of Cytogenetics and Molecular Genetics, and **Julie Woolworth, PhD**, Associate Director of the Molecular Pathology Laboratory. The CLIA-certified laboratory uses state-of-the-art next-generation sequencing (NGS) to screen biopsy samples from select cancer patients against a panel of 26 known oncogenes for which targeted therapies have been developed.

The MiSeq desktop sequencer (Illumina; San Diego, CA) used in the clinical genomics laboratory is the "kid brother" of HiSeq 2500, Illumina's high-throughput sequencer, which was recently acquired by the Center for Genomic Medicine for more complex research and clinical applications. Desktop sequencers such as the MiSeq are ideal for the clinical diagnostic laboratory because they offer the expanded sequencing ability of NGS together with practical advantages: they do not take up much space, provide user-friendly interfaces, automate many of the required steps for sequencing, and incorporate bioinformatics software that provides easy-to-interpret and actionable reports for clinicians.

Screening results can help clinicians to make treatment decisions. For example, targeted therapies would likely be more effective and have fewer side effects in patients found to have one of the mutations, whereas conventional chemotherapy would be the treatment of choice for patients without any of the mutations. Genomics screening can also identify resistance mutations that are predictive of poor response to targeted therapies, sparing patients unnecessary expense.



Genomics screening is not indicated in all cancer patients; it makes most sense in cancers for which clear targets have been identified and for which effective targeted therapies exist. Initial plans at MUSC are to screen most patients with colon cancer and all patients with non–small cell lung cancer or melanoma, all of which are cancers with identified targets and available targeted therapies. Patients whose cancer recurs after conventional chemotherapy and patients with metastatic disease would also be screened.

Targeted Therapies

Interest in targeted therapies has grown as researchers have realized that cancer is not a single disease entity, as once thought, but a plurality of subtypes, many of which are associated with characteristic mutations. To paraphrase Leo Tolstoy's famous opening line to Anna Karenina, healthy cells are all alike; every cancer subtype is unhealthy in its own way.

More than four decades after Richard Nixon declared a war on cancer with the National Cancer Act of 1971, mortality due to cancer in those aged forty and older remains high, leading many to believe that a shift from conventional chemotherapies to more targeted therapies will be necessary before real progress can be made. The successful sequencing of the human genome, the current efforts by the Cancer Genome Atlas to sequence the genome of many cancer subtypes, and rapid advances in sequencing technology have further fueled interest in these targeted therapies. Conventional chemotherapy and radiotherapy take broad aim at cancer, trying to kill as many cancerous cells as possible but inevitably inflicting collateral damage on healthy ones as well. In contrast, a targeted therapy attempts to disrupt oncogene-activated signaling pathways that promote the growth and spread of tumor. For instance, 10% of patients with non–small cell lung cancer have tumors with a mutation in the epidermal growth factor receptor (EGFR) that renders them susceptible to the small molecule drug erlotinib. These patients are very likely to benefit from targeted therapy with erlotinib, whereas those without the mutation would not.

According to **Stephen P. Ethier, PhD**, Interim Director of the Center for Genomic Medicine at MUSC, "These targeted therapies either work incredibly well or they work not at all—that's why the genetic testing is essential."

Clinical Genomics Testing and Clinical Trials

Genomics-based drug development challenges some of the basic assumptions of traditional clinical trials, which were developed to test more conventional, broad-based therapeutic regimens. Traditionally, the gold standard for proving efficacy was evidence of treatment response in phase 3 trials that recruited large numbers of patients with cancer of a single tissue (e.g., breast cancer) in order to attain sufficient statistical power. When tested in appropriately selected patients, those with the relevant mutation, targeted therapies have much higher response rates and can attain statistical power with far fewer trial participants. Pharmaceutical companies have now begun to develop targeted therapies and the diagnostics needed to identify appropriate patients simultaneously.

For many genomics experts, the current clinical trial system is illsuited to bringing cutting-edge targeted therapies to the patients who need them. Oncogenes identified by genomic sequencing are often associated with more than one type of cancer; for example, the HER2 oncogene is associated with breast, ovarian, and lung cancers, among others. However, the efficacy of the therapy has only been proven in phase 3 clinical trials for breast cancer. A patient with HER2+ Ovarian cancer could only be offered the treatment off-label, without hope of reimbursement, likely making it prohibitively expensive.

Dr. Ethier believes that this needs to change if we are to realize the promise of genomic screening: "There is a mindset in the community that the tissue of origin trumps the oncogene. And people like me are trying to flip this around and say that the oncogene is everything when it comes to targeted drugs—it trumps the tissue of origin." In his view, the U.S. Food and Drug Administration must revamp the clinical trials process so that therapies that prove effective against oncogenes in one setting can be used in other patients with that oncogene, regardless of tissue of origin, but this does need to be done in a clinical trial setting.

Although the clinical genomics laboratory is currently using a commercial panel of mutations for its screens, Dr. Wolff plans to create customized panels in the future, in part to attract more clinical trials of targeted therapies to MUSC. She is collaborating with **Carolyn D. Britten, M.D.**, Director of the Phase 1 Clinical Trials Program at MUSC's Hollings Cancer Center, to develop diagnostics for targeted therapies just entering phase 1 trials. Once pharmaceutical companies realize that such diagnostic testing is available to identify patients with the targeted mutation, they will be more likely to open phase 1 trials at MUSC, making some of the newest and most cutting-edge treatments available to South Carolinians. MUSC could even become the central genomics testing site for some of these studies.

Realizing the Promise of Personalized Medicine At Last

Fifteen years have passed since personalized medicine was first heralded as the future of medicine, and its promise has not been realized as quickly as many predicted, largely because the technology seemed out of reach for many health care institutions and the expense was prohibitive.

However, the cost of genomic sequencing has been decreasing even as its reach has been expanding. Next-generation sequencing (NGS), the development of which was spurred by efforts to sequence the human genome, can generate far more genetic data far more quickly and at a lesser cost than traditional sequencing technologies such as Sanger sequencing and DNA microarrays. The sequencing of the 3 billion base pairs of the human genome required several years using the older technology at a cost of about $13 billion; in contrast, the latest iterations of NGS platforms such as the HiSeq 2500 (Illumina, San Diego, CA) can sequence that number of base pairs in 25 hours for around $1000. NGS can sequence exponentially more base pairs than previous techniques because it can simultaneously analyze millions of DNA fragments and because, unlike those older technologies, it does not require decoupling of the sequencing and detection steps (i.e., they can occur simultaneously, not sequentially) or the use of a probe (sequence segment) that could bias results. According to Dr. Wolff: "The nice thing about this is that when we have lots and lots of copies of the pieces of DNA, we can reassemble them and look at the entire genome. It gives us higher fidelity of results and it's a lot faster." **Gary T. Hardiman**, PhD, the new Director of the Informatics Core for MUSC's Center for Genomic Medicine, not surprisingly reaches for an IT analogy when describing the potential of NGS: "NGS takes you away from technologies like microarrays and replaces this analog technology with digital technology. In the past, we were interrogating just a small region of each transcript delineated by a 60-70-base pair probe and now we can sequence across the entire transcript."

Rapid advances in NGS technology promise to one day soon translate into care that is truly tailored to the needs of the individual patient, especially as whole-genome sequencing becomes more feasible in the clinic. Researchers with The Cancer Genome Atlas project are using NGS technology to sequence the genome of many subtypes of cancer, spurring research to develop new therapies against identified targets and speeding a much wider-scale implementation of targeted therapies in clinical practice. The rapid availability of robust genomics data will also be a boon to pharmacogenomics, enabling better prediction not only of whether a person will likely respond to a therapy but also whether they are likely to develop side effects. The pharmaceutical industry, which has been somewhat reluctant to embrace personalized medicine and targeted therapies, has begun to warm to it as NGS identifies new uses for some of their older drugs and identifies subpopulations in which drugs they once abandoned because of disappointing clinical trial results might prove safe and efficacious.

It is not surprising that early genomics efforts have focused on cancer. Characterized by mutations of a patient's own healthy cells into lethal ones, cancer is in some ways the most personal of diseases. Next-generation sequencing offers a better understanding of these mutations in a clinically relevant timeframe and offers to identify therapies for cancer patients that are at once more effective and less toxic because they are profoundly personal.

GLOSSARY

Bioinformatics/Computational Genomics: Use of computational and statistical analysis to determine the biological relevance of genomic sequencing data.

ChIP Sequencing: A combination of chromatin immunoprecipitation and next-generation sequencing that can precisely identify binding sites for proteins.

Epigenetics: Heritable, functionally relevant changes in gene activity, possibly due to environmental pressures, that do not involve sequence changes. Examples are DNA methylation and histone modification.

Exome: The portion of the genome that codes for protein production. Sequencing of the exome can be a time-and cost-efficient alternative to sequencing of the whole genome when screening for mutations.

Genome: The totality of the genetic material of an organism, usually encoded as DNA.

Metagenomics: The genomic analysis of the viral and bacterial communities resident in a human and their potential links to disease, especially those such as IBD that relate to disruptions of a microenvironment.

Mutation: A change to the nucleotide sequence of a gene

Nucleic Acid Sequence: A succession of letters (GACT) that indicate the order of nucleotides within a DNA molecule.

Oncogene: Mutated forms of normal cellular genes (proto-oncogenes) that, when activated, are capable of transforming normal cells into cancerous ones.

Next-Generation Sequencing: Also known as massively parallel sequencing, next-generation sequencing can analyze millions of loci simultaneously, providing far more comprehensive genomics data than previous technologies such as microarrays and Sanger sequencing and without the need for a probe that can bias results.

Pharmacogenomics: The use of genomics screening data to predict a drug's efficacy and side effect profile in an individual.

Single-Nucleotide Variant: A one-letter (one-nucleotide) variation in the nucleic acid sequence of a gene

Targeted Therapy: A drug or immunotherapeutic therapy that has been developed to precisely target and disrupt cancer-promoting cellular signaling pathways in cancer subtypes associated with a particular gene mutation.

Whole-Genome Sequencing: A technique for obtaining the complete DNA sequence of an organism's genome at a single time.

Reprinted from the Summer 2014 Issue of Progressnotes, MUSC's Medical Magazine.
Available at MUSChealth.com/progressnotes

Sarah Simpson

Ashley Hall Student

In Recognition of Successfully Completing

2014 Summer Internship

Department of

Pathology and Laboratory Medicine

May 19 – 29, 2014

PATHOLOGY AND LABORATORY MEDICINE WINS

- *Latino American Who's Who Recognizes* ***Lee Marie Tormos, M.D.*** *at the link below:*

http://latinwhoswho.net/press/latino-american-whos-who-recognizes-lee-marie-tormos-md/

- ***David Turner, Ph.D.'s*** *Lab had a feature article in the Catalyst at the link below:*

http://academicdepartments.musc.edu/catalyst/archives/2014/6-6AGES.html

- ***Steve Ethier, Ph.D.*** *article in the Post & Courier at the link below:*

http://www.postandcourier.com/article/20140609/PC1211/140609273

- ***Julie Woolworth, Ph.D.,*** *passed her Technical Supervisor board examination in Molecular Diagnostics offered through American Board of Bio analysis (ABB). She took the exam in May of this year. She now has a few more initials after her title:*

Dr. Julie Woolworth Hirschhorn, Ph.D., TS(ABB)

Nomination:
You are the expert of EM! Great friend and good teacher!

Other Nominees: Molly Diaz, Brent Grimball, Dolly Hope, Jarvis Jenkins, Sonya Jordan, Teresa Kennedy, Linda McCarson, Kenyaria Noble, Tyrish Page, Joe Rozier, Lori Roten, and Trudie Shingledecker,

Nancy Smythe

Research Specialist II

ARRIVALS / DEPARTURES

ARRIVALS:

First Year Residents: Arrived 7/1/14

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

Fellows: Arrived 7/1/14

- **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. - 1st day will be 7/14/14
  Julie Robinson, M.D.

ARRIVALS Cont'd:

- ◊ Kenyara Noble arrived in Dr. Lang's lab as an RSI on 5/12/14
- ◊ Sheng Haibin arrived in Dr. Lang's lab as a visiting scholar on 5/23/14
- ◊ Xin Liu arrived in Dr. Lang's lab as a visiting scholar on 6/2/14

DEPARTURES:

Last Day—6/30/14

- Joseph Bergeron, M.D. — Cytopath Fellow
- Courtney Ingram, M.D.—Cytopath Fellow
- Kate Lindsey, M.D. —Cytopath Fellow
- Jessica Sugianto, M.D. — Dermpath Fellow
- Darren Monroe, M.D. — Forensic Fellow
- Kalli Faulkner, D.O. —Hematopath Fellow
- Tariq Rashid—Post-Sophomore Fellow
- Keels Allen, M.D.— Resident
- Sarah Brooks, M.D.—Resident
- Christina Stallworth, M.D. Resident

- ◊ Christopher Attaway left Dr. Smits' lab as an RSI on 5/23/14
- ◊ Blake Hayes left Dr. Cheung's lab as a Post Doc on 6-9-14
- ◊ Phillip Sobolesky left Dr. Moussa's lab as a PhD Student on 6/15/14

CONGRATULATIONS!

To: Daniel Skipper, M.D.
1st Year Resident

To: Lourdes Nogueira,
RSI in Dr. Findlay's Lab

IT'S TB Time!

TB Placement
Tuesday, July 22, 2014

7:00 –9:00 AM, RM 223 CH
AND
1:30 – 3:30 PM, RM 204 CH

TB Reading
Thursday, July 24, 2014

7:00 – 9:00 AM, RM 223 CH
AND
1:30 – 3:30 PM, RM 204 CH

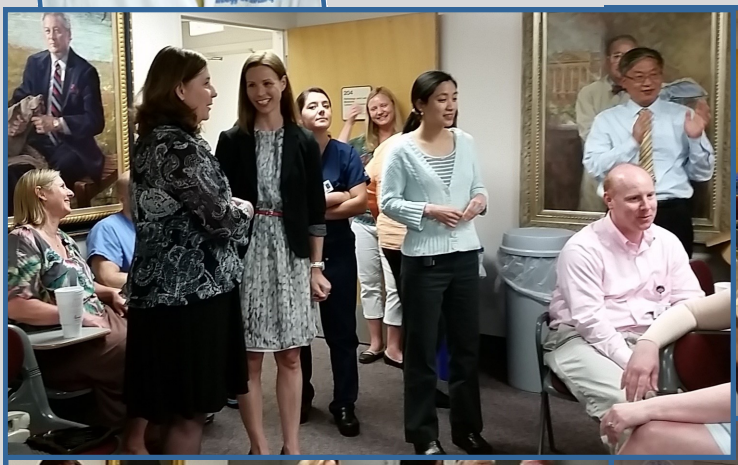
If you have had a positive skin test in the past, please pick up a form from your manager or from Marla Lockhart in room 335CH. Please complete the form and return to your manager or Marla Lockhart.
If you have had an allergic skin reaction to a previous tb skin test, there is an alternative method available to administer your tb test, just ask the nurse administering the test.

* PLEASE NOTE: IF YOU ARE UNABLE TO ATTEND THE ABOVE EVENTS, EMPLOYEES ARE WELCOME TO WALK-IN AT EMPLOYEE HEALTH SERVICES FOR THEIR ANNUAL TUBERCULOSIS SKIN TEST (TST) MONDAY THROUGH WEDNESDAY AND FRIDAY FROM 7:30 AM TO 3:30 PM.

FAREWELL AND BEST WISHES!

Anne Bartlett, M.D.

Michael Caplan, M.D.



RESEARCH DIVISION UPDATE

Statistics for the Division of Research from April through June.
Twenty Three grant proposals were submitted requesting $3,632,361
in total first year costs.
Also, during this period ten grants were awarded totaling $1,660,422.

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

SUBMITTED 4/1/2014 – 6/30/2014:

Annamalai, Bala, Ph.D.
Title: Development of S_Nitrothiol-based Therapy for Late0Onset of Alsheimer's Disease $63,368 – Proposed Start Date 6/1/14

Steven L. Carroll, M.D., Ph.D.
Title: Identification of neurofibroma and MPNST specific exosome-associated marker as early detectors of malignant transformation $13,000 – Proposed Start Date 4/15/14

Steve Ethier, Ph.D.
Title: Breast Cancer Oncogenes on the 8p11 Amplicon $342,977 – Proposed Start Date 6/1/14

Steve Ethier, Ph.D.
Title: Oncogenic Signaling Network in Triple Negative Breast Cancer $373,750 – Proposed Start Date 4/1/15

Hainan Lang, M.D., Ph.D.
Title: Auditory Nerve Degeneration and Repair $368,750 – Proposed Start Date 7/1/14

Hainan Lang, M.D., Ph.D.
Title: Auditory Nerve Degeneration and Repair (OMIC-supplement) $70,000 – Proposed Start Date 9/1/14

Meenal Mehrotra, M.D., Ph.D.
Title: Role of HSCs in Establishing the Osteosarcoma Microenvironment $198,000– Proposed Start Date 1/1/2015

Frederick Nolte, Ph.D.
Title: CTP0005-De-Identified Residual Blood Culture Sample Collection $24,867 – Proposed Start Date 9/1/14

Chandrakala Puligilla Ph.D.
Title: MEKK Signaling $10,000 – Proposed Start Date 7/1/14

Chandrakala Puligilla Ph.D.
Title: Role of SOX2 in Specification of Prosensory and Hair Cell Fate in Mouse Cochlea (OMIC-Supplement) $70,000 – Proposed Start Date 9/1/14

Bradley Schulte, Ph.D.
Title: Experimental and Clinical Studies of Presbyacusis (OMIC-supplement) $68,800– Proposed Start Date 9/1/14

Suhua Sha, M.D.
Title: A Rapid Assay for RSA Targeted Drugs $64,285 Proposed Start Date 5/1/2014

Suhua Sha, M.D.
Title: Molecular Mechanisms in Noise-Induced Hearing Loss $373,750 Proposed Start Date 4/1/15

Demetri Spyropoulos, Ph.D.
Title: ECM Proteins for Preservation of Viability, Attachment and Phenotype during and after Cryopreservation $74,756 – Proposed Start Date 10/1/14

Demetri Spyropoulos, Ph.D.
Title: Cryopreserved Whale iPCSs for Rapid, Highly Sensitive Screening for Obesogens $89,985– Proposed Start Date 10/1/14

Demetri Spyropoulos, Ph.D.
Title: Cryopreservation of Cell Viability and Architecture in Various Tissues $138,155– Proposed Start Date 10/1/14

David Turner, Ph.D.
Title: Targeting HSC-Derived Circulating Fibroblast Precursors in Pulmonary Fibrosis 8,474– Proposed Start Date 6/1/14

David Turner, Ph.D.
Title: PQ3: AGEs and Race Specific Tumor Immune Response in Prostate Cancer $224,250– Proposed Start Date 3/1/15

RESEARCH DIVISION UPDATE, continued

SUBMITTED 4/1/2014 – 6/30/2014 Cont'd:

David Turner, Ph.D.
Title: AGEs: A Consequence of Disparity Leading to Oxidative Stress in Prostate Cancer $384,513– Proposed Start Date 4/1/15

Yong Wang, Ph.D.
Title: The Response of Cancer Stem Cells to Radiation-Induced Senescence $373,750– Proposed Start Date 12/1/14

Yong Wang, Ph.D.
Title: Sensitization of Cancer Stem Cells to Radiotherapy by miR-34a $224,250– Proposed Start Date 4/1/15

Je-seong Won, Ph.D.
Title: Development of S_Nitrothiol-based Therapy for Late0Onset of Alsheimer's Disease $42,885– Proposed Start Date 5/1/14

Ying Xiong, Ph.D.
Title: Targeting HSC-Derived Circulating Fibroblast Precursors in Pulmonary Fibrosis $29,796– Proposed Start Date 6/1/14

AWARDED 4/1/2014 – 6/30/2014:

Annamalai, Bala, Ph.D.
Title: Development of S_Nitrothiol-based Therapy for Late Onset of Alzheimer's Disease $63,368 – Start Date 6/1/14

Steven L. Carroll, M.D., Ph.D.
Title: Identification of neurofibroma and MPNST specific exosome-associated marker as early detectors of malignant transformation $13,000 – Start Date 4/15/14

Steve Ethier, Ph.D.
Title: Breast Cancer Oncogenes on the 8p11 $332,687– Start Date 6/1/14

Hainan Lang, M.D., Ph.D.
Title: Auditory Nerve Degeneration and Repair $368,750 – Start Date 7/1/14

Amanda LaRue, Ph.D.
Title: Hematopoietic Stem Cell-Derived Carcinoma Associated Fibroblasts in tumors $18,302 – Start Date 7/1/14

Frederick Nolte, Ph.D.
Title: CTP0005-De-Identified Residual Blood Culture Sample Collection $24,867 – Start Date 9/1/14

Avtar Singh, M.D.
Title: Mechanisms of Krabbe Disease Pathobiology and Therapy $319,430– Start Date 4/1/14

Avtar Singh, M.D.
Title: Nitrosylation Mechanisms for Protection Against Neurovascular Inflammatory Injury $319,430– Start Date 5/1/14

David Turner, Ph.D.
Title: Glycation as a Mechanism Promoting Cancer Disparity $157,704– Start Date 4/1/14

Je-seong Won, Ph.D.
Title: Development of S_Nitrothiol-based Therapy for Late Onset of Alzheimer's Disease $42,885– Start Date 5/1/14

FACULTY FOCUS

CHRISTINE PAPADEA, PH.D
PROFESSOR EMERITUS

Christine Papadea, Ph.D. as Professor Emeritus of Pathology and Laboratory Medicine was recognized by the Department of Pathology and Laboratory Medicine for her appreciation and dedication to Medical Education and the Restoration of the Gordan R. Hennigar Pathology Museum. Dr. Papadea retired from MUSC in August, 2008. She has provided many years of distinguished service to the University.

Dr. Papadea is a Clinical Chemist with a national reputation for excellence in the field, particularly in the area of clinical application of mass spectroscopy. Due to her efforts, MUSC was an early adopter of this technology for the measurement of a variety of important and diverse analytes, including immunosuppressant drugs and vitamin D.

During her career here she worked tirelessly to serve physicians and patients through her efforts as Associate Director and Director of our Clinical Chemistry Laboratory. Her hard work and high standards are legendary, and had a direct impact of the quality of service delivered by that Division of Laboratory Medicine. She also served as an effective clinical consultant helping clinicians with question and problems related to laboratory tests.

Dr. Papadea also made important contributions to our Residency Training Program in Clinical Chemistry. She gave freely of her time to all of our residents, supervising their rotations, giving lectures, and serving as a research mentor. In her capacity as a research mentor she helped numerous residents with translational research projects that led to abstract presentations at national meetings and publications.

In her retirement she continues to make contributioins to MUSC as a volunteer. She transcribes historical manuscripts into an electronic format for the Waring Library Society and is assisting with a joint project between our Department and the Waring Library Society to clean, restore, preserve, and digitize its historical specimen collection.

Dr. Papadea made significant contributions to her field, our Department, and the University during her career, and we wish to provide her with this final accolade for her tireless pursuit of excellence in clinical service, education, and research.

BOX - ONLINE FILE SHARING

By: Tony Eisenhart

Box is an online file sharing system that is:

- Secure and compliant
- Provides a place for documents to live
- Restrictive but open to non-NetID holders
- Easy to use

Policies and Guidelines You Need to Know before Using Box:

Computer Use Policy

Social Media Guidelines

Data Protection Policy

Sanctions Policy

Training

Access to Box will not be granted until training is completed.

Box training will take about 30 minutes to complete. **Training is necessary even if you do not deal with protected data.** Since almost all MUSC files can be considered at least "restricted data", you need to know how to protect the privacy and safety of our patients, students, and employees. "I didn't know" will NOT be good enough.

Training is broken into three parts:

- Purpose and Responsibilities Overview
- Collaborators and Inheritance
- Basic Responsible Box Use

Each module should be taken in order. The information in the trainings modules are available on this site should you need to refer to it at a later point.

Directions:

Go to CATTS -> Self-Enroll for electronic sessions, and select "Box User". You'll be prompted to register for the three sessions.

When you are done with the sessions and quizzes, a Box folder will be created for you.

It will use your MUSC email address and NetID password, so you don't have to set up another account.

Signing an additional security agreement for Box is not required because your completion of training means acceptance.

Box Overview - Purpose and Responsibilities

MUSC's Box subscription is designed to balance the ease of use you desire with the protections MUSC demands. There's no denying cloud-based storage is very easy to use. And it's seductive to believe anything that makes it easier for you to do your work must be good for MUSC.

But the reality is the data used is not yours and MUSC has legal and ethical responsibilities for it.

Box is NOT dropbox (or GoogleDocs or Amazon Cloud Drive or iCloud)

MUSC has signed a "business associate agreement" (BAA) with Box so that, with additional security safeguards you can share and collaborate on protected data. Licenses with Dropbox do not cover protected data.

Box is NOT for personal use

In other words, you will not share or store your personal files, such as family photographs or personal records (like tax returns), in your MUSC Box folder. If people collaborating on files you provided need to do so after you leave MUSC, it will be easy to transfer those folders to someone within MUSC.

Circumstances where using Box works best:

- Not all of the participants have MUSC NetIDs
- Those external to MUSC don't mind signing up for a Box account or already have one
- The data can be changed by at least some of the people sharing the folder
- Some work on the files will be done from off-campus devices, like a computer at home
- You don't mind managing groups and access limits on your own

It's OK if the access to your folders is suspended the day you leave MUSC and the data itself is deleted 90 days later – or you remember to designate a new owner before your last day.

Box—Online File Sharing, Cont'd:

Circumstances where there are better options than Box:

- If everyone will access the data from an MUSC location (e.g., on campus; regional clinic) - the "N:" or "U: drives", a homeroom share, or a Sharepoint site will work better
- If your data must remain available to other MUSC NetID holders after you leave the institution - the "N:" or "U: drives", a homeroom share, or a Sharepoint site will work better
- If you cannot tolerate lack of access to the internet

If you're simply forwarding a file to an external user - FileLocker will work better

MUSC's Three Classes of data:

MUSC's policies define three classifications of data, according to sensitivity. These three classes are summarized as follows:

MUSC Public – No restriction on access

MUSC Restricted - Information that should not be available to the general public, but is not subject to HIPAA or other privacy laws

MUSC Protected - Personally identifiable information that is subject to privacy laws, including all "PHI" as defined by HIPAA

It is VERY important that you know the rules for different kinds of data. MUSC's policies defines some important principles for data protection.

Key Points:

- MUSC Protected data SHOULD NOT be stored on an end-user device such as a laptop, but if there is an unavoidable need, then encryption and other security controls need to be in place.

MUSC Protected data should NEVER be stored in an unapproved cloud service.

Ownership and Collaborators

Key Policies

If your intended collaborator has an MUSC NetID, then that person must also complete Box training before accepting the invitation.

If you knowingly invite an MUSC NetID holder but use another email address, you and the intended collaborator (once accepted) are in violation of MUSC's Computer Use Policy.

Ownership

All of the folders you create in Box, whether for a program or college or study – that is, for an effort that will continue without you – will be associated with YOU.

When you leave MUSC, we will turn off all access to your folders – unless you find another owner before your last day. Transferring ownership is as simple as sending a request to helpdesk@musc.edu.

Collaborators

Collaborators are people you give access to view and/or edit files in your Box folders. Anyone who is helping you fulfill at least one of MUSC's missions can become a collaborator.

It doesn't matter if the collaborator is also an MUSC faculty member, employee, or student, YOU will bear responsibility for your collaborators' actions.

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- You will remove the person's access as soon as the collaboration need ends
- Misrepresentation of the collaborator's justification for access to any resource will be subject to disciplinary action.
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Next-Generation Sequencing is Only Limited by the Imagination

By: Robert Wilson, Ph.D.

The Hollings Cancer Center Genomics Core Laboratory has been up and running for about two years now and we have been instrumental in working with a number of research collaborations.

Genomics covers a broad aspect of organisms' blueprints. The genome is quite complex. Areas of research cover whole genome mutation analysis, whole exome mutation analysis, chromatin structure, gene expression, RNA protein interactions and much more.

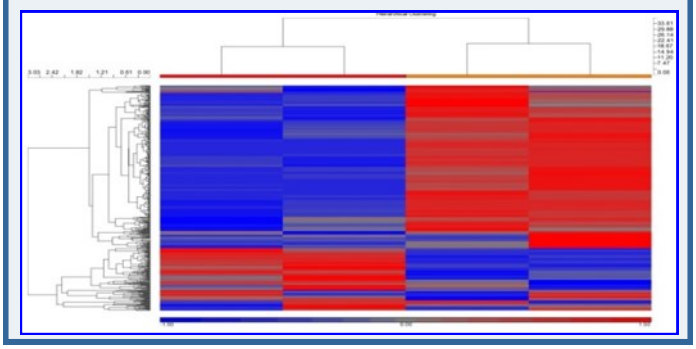
The human genome has 3 billion base pairs of DNA making up our chromosomes. To put this into perspective, 1 million seconds is 11.5 days and 1 billion seconds is 11,606 days or 31.7 years. Our most recent acquisition was the Illumina HiSeq2500 which has the latest hardware and software to run version 4 sequencing. The HiSeq2500 can sequence 1 whole human genome in 27 hours or 10 human genomes in 6 days.

These are very exciting times for basic research and clinical care. Next-Generation Sequencing (NGS) is done by massively parallel sequencing. In other words, sequencing that is done on millions of different unique DNA strands at the same time. The advent of NGS has changed the landscape of research and is beginning to revolutionize medicine.

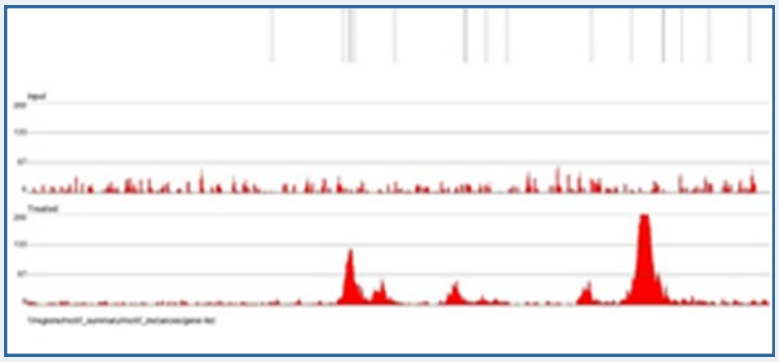
In the clinical setting, there have been multiple inspirational accounts of NGS saving lives. Recently highlighted in a New York Times article and published in NEJM, 2014 Jun 4, NGS saved the life of a 14-year-old boy that had undergone an unrevealing yearlong clinical course. The boy had a fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. An extensive infectious disease workup didn't reveal any infection. For multiple reasons, CSF was sent for pathogen detection by NGS which revealed a Leptospira santarosai infection. A course of high-dose intravenous penicillin G was given and the boy recovered in 7 days.

In another example, whole exome sequencing (WES) was used to determine the etiology of a severe case of pediatric-onset inflammatory bowel disease (Genomics. 2013 Nov-Dec). Due to the WES results, the patient underwent hematopoietic stem cell transplantation and demonstrated marked clinical improvement.

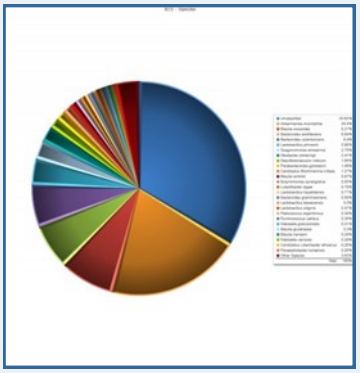
At MUSC multiple gene expression whole transcriptome sequencing (RNA-Seq) studies are being conducted with help of the core. These range from looking at the effects of drug treatment in cancer cell lines to Vitamin D supplementation in human prostate to drug addiction in rats. Below is an example heatmap of ± hormone treatment in mice:



Another area of interest has been in DNA/Protein interaction. One of the ways to determine what DNA elements are involved in the interaction of a DNA binding protein(s), is utilizing chromatin immunoprecipitation sequencing (ChIP-Seq). An example of protein binding sites are shown by peaks of enriched binding sequences:



Recently we initiated NGS for identifying bacteria species in fecal samples. Below is a diagram of bacterial species identified in one sample. This type of analysis can be done from any sample type.



Other sequencing technologies performed by the core have been:

- Whole genome sequencing
- Whole exome sequencing
- RIP-Seq for profiling protein/RNA interactions
- Ribosome profiling for determining mRNA translational state
- Histone modification/chromatin interactions
- High throughput shRNA screening
- High throughput PCR amplicon screening
- MicroRNA sequencing
- Targeted amplicon sequencing

Above is just the tip of the iceberg what can be done with NGS. There are about 20 protocols published studying completely different aspects of RNA transcription including RNA structure. There are similar amounts published for a multitude of epigenetic modifications including DNA methylation and DNA/protein interactions.

The HCC Genomics core isn't restricted to human samples. We have sequenced samples from humans, rats, mice, alligators, dolphin, whale, fish, Drosophila and wasp.

Future Plans

Recently in the clinical setting, MUSC's Cytogenetics and Molecular Pathology Laboratories initiated a 26 gene cancer panel utilizing NGS. In collaboration with the Cytogenetics and Molecular Pathology Laboratories, we plan on bringing whole exome sequencing into the clinical setting from patient samples to help determine diagnosis and treatment.

If you have any questions about NGS, contact me at 6-2217 or wilsorc@musc.edu.

Identification of Susceptibility Genes for Age-Related Hearing Loss

By: Bradley A. Schulte, Ph.D.

Currently some 28 million Americans have impaired hearing and approximately 75% of these individuals are over the age of 55 (Dawson and Adams, 1987; Gates and Mills, 2005). Age-related hearing loss (presbyacusis) thus constitutes a significant and chronic health problem diminishing the quality of life of a large portion of the older adult population. Defining the pathophysiological changes and the specific molecular alterations associated with age-related hearing loss has been a major focus of our laboratory over the past 25 years. This work has included studies of both animal models and human subjects in close collaboration with several researchers in the Department of Otolaryngology and Head and Neck Surgery. Funding for these studies has been provided by a large multi-project NIH grant entitled "Experimental and Clinical Studies of Presbyacusis" along with several R01 grants to individual investigators.

Significant progress has been made in our understanding of the pathological and functional changes that occur in the inner ear with age using animal models. However, little is known about the specific physiologic, genetic, molecular and cellular defects associated with presbyacusis in humans. Such information is essential for advancing the diagnosis and treatment of age-related hearing loss and depends importantly on data that can be obtained from studies of human temporal bones. However, histopathological analyses of alterations in temporal bones from older adult humans thought to have age-related hearing loss have, for the most part, provided inconclusive data. For many years, four categories of presbyacusis were commonly accepted (Schuknecht, 1974); 1) sensory, characterized by atrophy and degeneration of sensory hair cells and supporting cells; 2) neural, typified by loss of spiral ganglion neurons; 3) metabolic, characterized by atrophy and degeneration of the lateral wall of the cochlea; and 4) mechanical, where the inner ear is hypothesized to change its conductive characteristics. Schuknecht and Gacek (1993) subsequently made significant revisions to their classification scheme, paraphrased as follow;: 1) sensory cell losses are the least important type of loss in the aged ear; 2) neuronal losses are consistent and predictable expressions of aging; and 3) atrophy of the stria vascularis is the predominant lesion of the aging ear. These conclusions, along with detailed electrophysiological and histopathological studies of our gerbil aging animal model (Tarnowski et al., 1991; Schulte and Schmiedt, 1992; Schmiedt et al., 2002; Mills et al., 2006; Lang et al., 2010), strongly support the thesis that presbyacusis is primarily a neural and metabolic/vascular disorder, rather than a sensory disorder.

Age-related hearing loss is a consequence of accumulated environmental injuries to the cochlea along with an intrinsic genetically controlled aging process, with as much as 55% of hearing losses in older adults being attributable to heritability (DeStefano et al., 2003). The large variability in the age of onset, rate of progression and the nature and severity of the hearing impairments make it difficult to attribute presbyacusis to a specific cause. However, this significant phenotypic variability and other characteristics strongly suggest that presbyacusis is a complex polygenic disorder possibly involving numerous alleles on multiple genes (Liu and Yan, 2007). Although evidence for a role of susceptibility genes is strong, few molecular genetic studies of presbyacusis have been performed and only one gene (GRM7) has achieved genome-wide significance (Friedman et al., 2009). Accordingly, a population-based cohort molecular genetic study is needed to provide information about genetic contributions to presbyacusis.

Image of Human Cochlea with Temporal Bone Removal

As mentioned above, one of the major reasons for the lack of progress in this area has been the extensive phenotypic variability in hearing loss among human subjects. We have recently developed a procedure to classify audiograms from human subjects into specific phenotypes based largely on studies from our and other laboratories on animal models of presbyacusis. Normal hearing requires the cooperative activity of many different cell types and tissues including neuroepithelial sensory hair cells, primary auditory neurons, highly specialized epithelial cells, fibrocytes in the lateral wall that generate ion gradients and the endocochlear potential, as well as specialized structural components, such as the basilar and tectorial membranes. Mutations in genes affecting the function of any of these cell types or membranes can result in hearing impairment as is reflected by the broad spectrum of pathological and biochemical changes reported in the aging ear. These changes, along with correlative electrophysiological studies, have provided the basis for our unique stratification of human audiograms into specific phenotypes. The availability of this extensive and expanding database containing well documented medical, noise and auditory function histories, and DNA samples from over 500 subjects of European ancestry over 55 years of age have placed us in a unique position to investigate genetic variants associated with presbyacusis. This database along with the development of a Genomics Core Sequencing Laboratory at MUSC and the recent acquisition of an Illumina HiSeq2500 high throughput platform, have enabled us to secure funding to perform a large scale genome-wide phenotype association study (GWAS).

This GWAS will initially evaluate a discovery cohort of 300 metabolic cases and 300 controls all of European ancestry. Cases and controls will undergo whole exome sequencing. Initial primary association tests will be performed on variants in over 100 carefully selected candidate genes. With a case-control study of 600 phenotyped European ancestry subjects, we will be powered to detect genotype relative risks as low as 1.66 for common variants with 80% poser and $\alpha = 0.0005$. Additional exploratory association tests will be conducted with exome-wide variants. Discoveries will be replicated in a new sample of 400 subjects collected over the next four years. Continuous phenotypes also will be explored for associations with candidate markers and any variants reaching genome-wide significance.

As mentioned above, little is known about the specific molecular and cellular defects associated with presbyacusis in humans. Thus as a final part of this study, in collaboration with Dr. Hainan Lang, the distribution of candidate gene products and changes in their expression patterns will be assessed with relation to pathological alterations and when available, functional phenotypes in human temporal bones. These analyses will be performed on existing and prospectively obtained specimens processed in two ways. One ear will be processed to enable qualitative and semiquantitative immunohistochemical, *in situ* hybridization and laser capture microdissection analyses of protein and gene expression. The second ear will be fixed and embedded in plastic to obtain correlative histopathological and morphometric data. Comparisons will be made among temporal bones from younger and older donors and from older donors with phenotypes suggestive of metabolic and sensory presbyacusis. Similar approaches will be used to perform correlative studies of the most promising genetic variants using an inbred mouse model of age-related hearing loss.

The identification of genetic variants underlying individual susceptibility to certain forms of presbyacusis is an essential first step to defining the biological pathways involved and the discovery of new molecular targets for the diagnosis, prevention and treatment of this debilitating handicap. It is gratifying that after many years of work we are finally in a position to provide answers to this important issue.

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2013-2014 END OF THE YEAR AWARDS

END OF YEAR AWARDS—CONT'D

CYTOPATH

DERMPATH

HEMATOPATH

FORENSIC PATH

SURGPATH

RESIDENT TEACHING AWARD

RESIDENTS

GRADUATE STUDENTS

UPCOMING MEETINGS

- **APC – Association of Pathology Chairs in Boston, MA - 7/8 - 7/11**
- **SEAPC—Southeastern APC Regional Meeting , Savannah, GA - 10/1 - 10/3**
- **SNO - Society for NeuroOncology Meeting, November 13 - 16, 2014**

ALL HANDS MEETING

TUESDAY, SEPTEMBER 16, 2014 - 9:30-10:30 AM - HCC120

Dean Pisano will give a Financial Update

DEPARTMENT HOLIDAY PARTY

Friday, December 19, 2014

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.

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