

# THE PATHWAY

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## stAGEs of Cancer

Grape compound could reduce cancer-linked molecule in the diet

BY SVER AUNE

Could a common byproduct of the Western diet thought to promote cancer be reduced pharmacologically? Researchers at MUSC Hollings Cancer Center are testing compounds designed to block advanced glycation end products (AGEs) in patients with metastatic breast cancer who are receiving endocrine therapy. The pilot trial is led by **Carolyn D. Britten, M.D.**, associate director for clinical investigations at Hollings, and inspired by the preclinical work of MUSC cancer biologist **David P. Turner, Ph.D.**

Scientists have known that patients with diabetes have high concentrations of AGEs in their blood. Yet Turner is among the first researchers to study how AGEs set the stage for cancer. AGEs accumulate in the body as a byproduct of breaking down sugar but are also found in red meats and fried and processed foods. Once in the body, they cause the formation of reactive oxygen species that can encourage the development and spread of cancer.

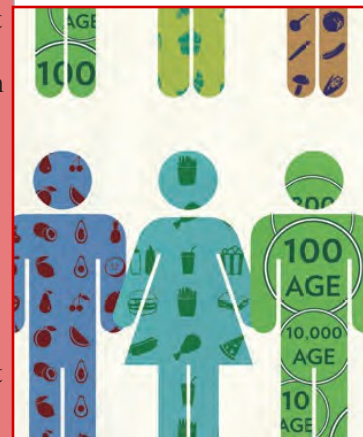
“AGEs are highly volatile and promote inflammatory and immune responses in the body,” says Turner. “We want to try to reduce AGEs in cancer patients because those responses may contribute to the return of cancer.”

Britten’s trial will test whether AGEs can be reduced pharmacologically with a compound isolated from grapes called oligomeric proanthocyanidin complex (OPC) in women with estrogen receptor–positive metastatic breast cancer. Patients must be receiving endocrine therapy to block the production of estrogen that is likely driving metastasis. Patients will take the oral hypoglycemic metformin along with OPC for 12 weeks. AGE concentration in the blood will be tracked before and after treatment to see if AGEs drop as a result of receiving OPC and metformin.

This follows preclinical studies by Turner that found that AGE levels were the highest in tumors of men with the worst prognosis for prostate cancer. A trial already underway in patients with prostate cancer, led by **Michael B. Lilly, M.D.**, associate director of translational research at Hollings, is also tracking the reduction of AGEs in men taking OPC. In a recently completed trial, Turner worked with **Marvella E. Ford, Ph.D.**, associate director of population sciences and cancer disparities, and **Gayenell Magwood, Ph.D.**, professor in the College of Nursing, and showed that exercise and a healthy diet can reduce AGE levels in breast cancer survivors. Turner was recently funded to conduct a dietary and physical intervention trial in prostate cancer survivors and to measure the effects of those interventions on AGE concentration. **PROGRESSNOTES FALL 2017 ISSUE**



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



### Inside this issue:

stAGEs of Cancer Article	1
Golden Apple Awards	2
Annual Service Awards	3
Thank you! & Congratulations	3
Graduate Studies Update	4
MUSC EARTH DAY	5
Research Division Update	6
2017 Holiday Celebration	7
Article by Dr. Spyropoulos	8-9
Article by Dr. Olar	9-10

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# CONGRATULATIONS!



## GOLDEN APPLE AWARDS

**Dr. Debra Hazen-Martin**

First Year  
Golden Apple  
Nominee



**Dr. Nicholas Batalis**

Second Year  
Golden Apple  
Nominee



**Dr. Sally Self**

Second Year  
Golden Apple  
Nominee



**Dr. Erin Presnell**  
Clinical Year Faculty  
Golden Apple  
Nominee



**Dr. Nicholas Batalis**  
COM2 Block 9  
Faculty Excellence  
Award Winner!



**Dr. Jerry Squire**  
COM2 Block 8  
Faculty Excellence  
Award Winner!



## UNIVERSITY SERVICE AWARD RECIPIENTS - 2017

DISPLAY NAME	HOME UNIT NAME	YRS HIRED	TITLE
JASON FLAMM	INFORMATION TECHNOLOGY	10	INFORMATION RESOURCE CONSULTANT
FREDERICK S. NOLTE, PH.D., D(ABMM), F(AAM)	CLINICAL PATHOLOGY	10	PROFESSOR & DIRECTOR, CLINICAL LABORATORIES
GAVIN WANG	RESEARCH	10	ASSISTANT PROFESSOR
SALLY SELF, M.D.	CLINICAL PATHOLOGY	30	PROFESSOR & DIRECTOR OF DIAGNOSTIC IMMUNOLOGY
JARVIS JENKINS	BUSINESS OFFICE	30	SUPPLY SPECIALIST II

## THANK YOU!!

**Phil Han MD, PhD (Clinical) & Gong Feng, MD, PhD (Anatomic)  
for the Team Coverage during the Winter Storm!!**

### WINTER STORM HITS CHARLESTON WITH ICE AND SNOW - JANUARY, 2018

Dr. Jerry Squires sent the following Thank you;

I wanted to send you just a quick note to commend Phil Han on his CP on-call coverage this past week. As you know he provided "A" team coverage during the winter storm, but even more importantly, he provided excellent support to the blood bank during a very difficult period. He was available and supportive to the blood bank technical staff and communicated with me appropriately and as needed. We have been experiencing a severe platelet shortage due to the weather conditions and the inability of the Red Cross to collect adequate numbers of donors. Phil worked with me, the clinical staff, and the blood bank staff to manage the platelet inventory as well as possible. In spite of the difficult situation he remained available and courteous, and made appropriate clinical decisions—and most perhaps importantly consulted with me as necessary. Phil did, in my opinion, an excellent job and represented the Pathology and Laboratory Medicine Department well.

## CONGRATULATIONS!

- ◆ One of our second year residents, **Dr. Jessica Snider**, recently found out that she was named the recipient of a competitive translational diagnostics advanced training award from the College of American Pathologists. This prestigious opportunity is only conveyed to 1 pathology resident across the country each year and will allow her to spend a month at Ventana Medical Systems in Tucson, AZ to learn about advancements in molecular pathology and oncology including developing novel histopathology assays (please see attached pdf for a more detailed description). This is a truly unique opportunity to receive training in aspects of pathology essentially only available through this program. It's been a few years since one of our residents has received any sort of travel award so I just wanted to check and see if there's anything else that needs to be done on our end to support her. Jessica has spoken with the coordinators at Ventana and is tentatively approved to rotate there in February 2018.
- ◆ **Dr. Hainan Lang** has accepted an invitation to serve as a member of the Communication Disorders Review Committee of the National Institute on Deafness and Other Communication Disorders (NIDCD) for a four-year term beginning July 1, 2017 and ending June 30, 2021.
- ◆ **Dr. Julie Hirschhorn** participated as a Judge in the Perry V. Halushka MUSC 2017 Research Day on Friday, November 3, 2017. She participated with 85 faculty and postdoctoral fellows that volunteered their time and talents as judges.
- ◆ **Dr. Su-Hua Sha** was invited to join the Ototoxicity Committee for the Department of Defense (DOD) Hearing Center of Excellence (HCE) Pharmaceutical Interventions of Hearing Loss (PIHL) Working Group.
- ◆ **Dr. Meenal Mehrotra's** abstract that she submitted for the American Association of Dental Research Annual Meeting has been accepted for an oral presentation. She has also been invited to Chair the Stem Cells and Regenerative Medicine Oral Session at the Annual Meeting.

**GRADUATE  
STUDIES  
UPDATE**

**NOVEMBER 15, 2017**

**Student Update**

**Student Research Day**

50% success rate in Awards this year

**Oral Awards**

Lauren McLean (Dr Smits) – 1<sup>st</sup> Place PhD

Ryan Kelly (Dr LaRue) – 2<sup>nd</sup> Place PhD

Clare Burton (Dr Findlay) – 2<sup>nd</sup> place Masters

**Poster Awards**

Lourdes Nogueira (Dr Findlay) – 1<sup>st</sup> Place Research Specialist

Kenyaria Noble (Dr Lang) – 2<sup>nd</sup> Place PhD

Clarisse Panganiban (Dr Lang) – 2<sup>nd</sup> place PhD

Jaime Randise (Dr Turner) – 2<sup>nd</sup> place Masters

**Qualifying exam Spring 2017**

All 3 students passed the written qualifying exam

Lauren McLean (Dr Smits)

Ralph Tanios (Dr Carroll)

Kenyaria Noble (Dr Lang)

**Master's Students**

Jon DiMaina (Dr Cheung) successfully defended his MS thesis

Bradley Krisanits (Dr Turner) and Laurel Black (Dr Carroll) successfully defended their MS thesis and both were accepted into the PhD program and have joined their respective MS mentors labs.

Master's Student Training Program student Jamie Mills (Dr Ethier) successfully defended her PhD thesis

PhD defense dates for Spring 2018 – TBA

Ryan Kelly (Dr LaRue)

LaShardai Brown (Dr Lang)

Alexandria Rutkovsky (Dr Ethier)

Ericka Smith (Dr Ethier)

**Council News**

Annual Evaluation Forms have been updated

Now includes a 1 page status report

Both forms are now live and online

# SAVE THE DATE

# MUSC EARTH DAY

Wednesday April 11th, 2018  
11am - 2pm | MUSC Horseshoe

Earth friendly vendors, food trucks,  
door prizes, farmers, craftsmen, & more







# RESEARCH DIVISION UPDATE

Statistics for the Division of Research from October-December thirteen grant proposals were submitted requesting \$3,734,548 in total first year costs. Also, during this period six grants was awarded totaling \$756,410.

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

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

## GRANT APPLICATIONS SUBMITTED - 10/1/2017 - 12/31/2017

Principal Investigator	Proposed Start Date	Title	Total 1st YR Dollars
Cheung, Hiu	7/1/2018	Targeting GAB2 oncogene in high-grade serous ovarian cancer	\$373,750
Ethier, Stephen	10/5/2017	Tandem duplicator phenotype and oncogenic signaling in triple negative breast cancer	\$777,100
Lang, Hainan	12/7/2017	Auditory Nerve Degeneration & Repair	\$539,346
Mehrotra, Meenal	11/1/2017	CD36-Sphingosine 1-Phosphate Axis in Osteosarcoma Progression	\$50,000
Mehrotra, Meenal	11/16/2017	Efficacy of Treg transplant as cellular therapy in a mouse model of Osteogenesis Imperfecta	\$74,750
Schandl, Cynthia	11/1/2017	Circulating tumor DNA as liquid biopsy in patients with stage IV solid tumors, as feasibility study at MUSC-HCC	\$49,713
Spyropoulos, Demetri	12/6/2017	RT170031 Preservation of Unsalvageable Debrided or Excised Traumatic Limb Injury Tissues for Later Reconstructive Surgeries	\$345,019
Spyropoulos, Demetri	10/16/2017	Genomic and Metagenomic Determinants of Obesogen Susceptibility in an Advanced Animal Model	\$25,000
Turner, David	10/26/2017	Strategies to Mitigate Advanced Glycation End products (AGEs) in Prostate Cancer	\$161,930
Wang, Gavin	10/5/2017	MYC Inhibition-Induced Cancer Stem Cell Depletion	\$371,230
Wang, Gavin	10/5/2017	Intracellular Signaling Network Analysis of Stress-Induced Stem Cell Senescence	\$371,230
Wang, Gavin	12/6/2017	BC171696 Elimination of Breast Cancer by Targeting the Lipid Metabolic Pathways	\$371,230
Won, Je-Seong	10/16/2017	Asymmetric dimethylarginine (ADMA) as a risk factor and biomarker for late-onset Alzheimer's Disease	\$224,250
<b>Total Proposals</b>	<b>13</b>		<b>\$3,734,548</b>

## GRANTS AWARDED - 10/1/2017 - 12/31/2017

Carroll, Steven	9/21/2017	SC Cancer Disparities Research Center (SC CaDRe) U54	\$31,213
Findlay, Victoria	9/21/2017	SC Cancer Disparities Research Center (SC CaDRe) U54	\$74,451
Turner, David	9/21/2017	SC Cancer Disparities Research Center (SC CaDRe) U54/Project 001	\$170,370
Turner, David	9/21/2017	SC Cancer Disparities Research Center (SC CaDRe) - AGE Shared Core/U54	\$112,279
Wilson, Dennis	9/21/2017	SC Cancer Disparities Research Education Core (SC CaDRe) U54	\$293,347
Sha, Suhua	12/1/2017	Nucleobase amino sugars with reduced ototoxicity - R41/Subaward	\$74,750
<b>Totals Awarded</b>	<b>6</b>		<b>\$756,410</b>

# 2017 HOLIDAY CELEBRATION







# Precision Medicine: Making it More Precise with Better Research Models

By Demetri D. Spyropoulos , Ph.D.

Precision or personalized medicine seeks to cure patients using tailor-made therapies. Why do we need precision medicine? Because one size doesn't always fit all! Patients with the same diagnosis can respond quite differently to the same therapy. In some cases, this can mean the difference between full recovery and death.

Why do patients respond so differently? It's not entirely clear yet, which is why we need better research models and further investigation. One idea is that similarly diagnosed diseases could have different root causes and different targets for therapies. And treating the root cause is usually a better fix than treating a symptom. There are many examples in which environmental conditions mimic or "phenocopy" diseases or traits caused by inherited or acquired genetic mutations. These often, but not exclusively, occur during development. For example, Himalayan rabbits, which are genetically white with black tail, nose and ears in temperate climates, can phenocopy rabbits that are genetically black if they are reared in cold climates.

The topic gets more complicated considering the great diversity in our inherited genetic susceptibilities and how our genetics interface with our complex history of environmental exposures. Mutations and gene variants, gene variant-by-gene variant interactions (genetic background), single and combinatorial exposures and gene-by-environment interactions all can complicate therapeutic outcomes. As alluded to with the rabbits, environmental conditions can range from temperature to acute and long-term toxic exposures. Of note, the variety and bulk quantity of synthetic chemicals produced has grown exponentially since WWII, in line with increases in neurological and cardiovascular diseases, diabetes, obesity, and cancers.

To fit these biomedical research needs, we use cell-, tissue- and animal-based models. Immortalized cell lines and "primary cells," those taken directly from the body, are the workhorses for assays and basic questions. For example, we use stem cells and "pre-adipocytes" (cells poised to become fat cells) to test for chemical "obesogens" that drive stem cells to fat cells (at the loss of bone or other cell types they could produce).

How a chemical impacts a cell line or primary cell on a petri dish in culture (*in vitro*), however, is not necessarily how it will impact a tissue or organ containing multiple interacting cell types or the body as a whole (*in vivo*). Cells, tissues and integrated systems in our bodies are highly resilient and repeatedly bounce back from insults. Well-functioning "homeostatic mechanisms" help us maintain or regain a state of equilibrium as we work through daily, seasonal, and age-related changes. Given generations of time, we can adapt to changing environments and other selective pressures. For example, healthy carriers of one copy of the sickle cell anemia gene mutation are more likely to survive malaria and more commonly live where malaria is most prevalent. Other disease-resistance gene mutation pairings include cholera-cystic fibrosis, tuberculosis-Tay-Sachs, and mycotic abortions-phenylketonuria, all of which likely became common by selective pressures in affected geographic regions.

We use genetically identical (inbred) rodent models to ask gene- and chemical-based *in vivo* questions. For example, how does the sickle cell anemia gene mutation bestow resistance to malaria? Mice carrying one copy of the sickle cell anemia gene mutation were generated and used to show that much higher activity of the Heme Oxygenase-1 enzyme and production of carbon monoxide were responsible for resistance to malaria. Sophisticated gene gain-of-function (transgenic), and knockout rodent models have shown us the roles of particular genes in health and pathology. These genetic models go as far as to allow us to turn a particular gene "on" or "off" in a particular cell type at a particular time. Our groups used such models, not only to show the gene's roles in healthy development and disease, but also to show that the same gene knockouts can be lethal or produce little effect depending on the inbred strains of mice used. This points to the fact that diverse genetic backgrounds ("modifier" genes in particular) can profoundly change the impact of a genetic mutation or variant or the ability of an environmental agent to phenocopy a genetic disorder.



Continued—

Using the inbred strain of mice most commonly studied for diet-induced obesity, we showed that the chemical obesogen that drives stem cells to fat cells *in vitro* is also a bona fide obesogen *in vivo*. Many pregnant women use this obesogen as a drug treatment for constipation. When pregnant mice are fed relatively the same doses, their offspring develop obesity and diabetes, even when fed regular diets. We are now going to test this obesogen in rodents that have the genetic diversity of people to find modifier genes that make them sensitive or resistant to this obesogen. Currently, half of all Americans are borderline diabetic or diabetic and by 2030 half of all Americans are projected to be obese or morbidly obese. Knowing the genetics of susceptibility and key chemical obesogens will likely help curb this trend.

Another level of complexity should also be addressed. Each of us carries on us and within us roughly 10-times more microbial cells than human cells. We have all kinds of microorganisms in our bodies all the time. When our state of equilibrium is out of whack, the kinds of microbes change and what the microbes put out into the body also change. Chronic inflammation and immune imbalances are associated with these changes. Such pathological microbial states can contribute to the origins of diseases and make diseases worse. For example, transfer of pathogenic microbes from the gut of an obese mouse to a non-obese mouse can cause obesity, even without altering diet or exercise. With “abiotic” (no microbes) and “gnotobiotic” (known microbe) models, we can control for these microbial communities in our studies.

New “genome editing” technology makes it easier for us to modify any gene sequence in any cell type of any organism. For example, some 80 test subjects infected with HIV have had the HIV receptor (CCR5) gene knocked out in their immune T cells using this new technology. This makes the patient healthy by making those T cells resistant to infection. Since these T cells are short lived, this treatment needs to be repeated periodically in each patient. This would be a permanent cure in these patients if the CCR5 receptor were knocked out in the blood stem cells that give rise to these T cells. Researchers, however, have approached such permanent fixes with caution because of the potential that this genome editing technology would produce “off target” mutations elsewhere in the genome that could lead to blood cell disorders, such as anemias and cancers. For this same reason, there is hesitation to correct mutations in human embryos and long-lived stem cells.

Finally, our lab has also developed technology to freeze away excised tissues from patients, such that when they are thawed they behave as if they were freshly isolated. With this “cryopreservation” technology we can thaw multiple patient’s tissues with the same pathology at once and test therapeutic efficacies in parallel out of the body (*ex vivo*) in organ cultures. Therapeutically responsive and unresponsive tissues can be probed to find distinguishing molecules or “biomarkers”. In this way, we could go to other patients with the same pathology and look to see if they had those biomarkers (e.g. in blood or saliva) indicating that they would be good candidates for that therapy. Novel therapeutics can also be developed in a similar manner. In this way, we seek to apply this new technology to patient-specific pre-clinical models. We’ve also applied it to lung transplantation, so that we can extend the survival and geographic range to find a recipient’s “perfect match” donor.

Certainly, the body is an exquisitely resilient mechanism and we are all the products of an unbroken chain of survivors of famines, plagues and a multitude of maladies. Nevertheless, our environment contains an unprecedented and exponentially growing bulk and variety of new synthetic chemicals that miscue the body and drive new maladies and phenocopies of existing ones. How we learn to recognize the chemical drivers, susceptible populations and pathologies inflicted, and proactively prevent and treat individuals on a case-by-case level is part of the challenge researchers face.

**USCAP**  
**Vancouver, Canada**  
**March 17-23, 2018**

**Pathology Spring Symposium**  
**East Beach Conference Center**  
**Kiawah Island**  
**April 17-21, 2018**

**Experimental Biology Annual Meeting**  
**San Diego, CA**  
**April 21-25, 2018**

## **UPCOMING MEETINGS**

**Association for Pathology Chairs**  
**Coronado, CA**  
**July 16-19, 2018**

**American Society for Clinical Pathology**  
**Baltimore, MD**  
**October 3-5, 2018**

# Genomic landscape of glioblastoma and clinical testing at MUSC

By Adriana Olar, M.D.

Glioblastoma (GB) is the most common and most aggressive diffuse glioma having a universally fatal outcome. Histologically graded WHO grade IV (out of IV) this tumor is typically encountered in White adult males and is less common in children. GB has a classical histology that does not offer further clues into its genotype (nowadays common fact in diagnostic oncologic pathology). This means that 2 different patients with histologically identical tumors may have totally different outcomes: one may have a prolonged overall survival (OS) sometimes exceeding several years and the other might have an accelerated disease course with short OS and possibly death in less than a year. Recent genomic advances in GB profiling outlined several prognostic disease subgroups and offered new clues into its biology. Since 2016, GB is diagnosed based on histology paired with results of molecular biomarkers. Testing for the recommended biomarkers is available in the Clinical Molecular Pathology Laboratory at MUSC. Below is a brief outline of the genomic landscape of adult and pediatric GB with an emphasis on the clinical course of disease. Most recent advances are summarized.

The presence or absence of IDH mutations now represents the first step into stratifying GB. IDH-wild-type GB (or primary GB) usually arises in the elderly *de novo*, in patients without a previous history of diffuse astrocytic glioma and has a dismal prognosis. IDH-mutant GB (or secondary GB) arises from histological progression of a lower-grade diffuse astrocytic glioma, usually in younger adults, and has an improved outcome. IDH1/2 mutation status is currently determined at MUSC by immunohistochemistry against the mutant protein IDH1-R132H (which represents the most common mutation in diffuse glioma) followed for negative samples by reflex sequencing for IDH1/2 – exon 4. IDH1/2 gene regions are part of a 50-gene panel and are interrogated by next-generation sequencing.

Based on expression profiles The 2010 Cancer Genome Atlas (TCGA) defined 4 GB subgroups in adult patients: the prognostically favorable proneural subgroup (associating IDH and TP53 mutations, PDGFRA amplifications, and the glioma-CpG island methylator phenotype – G-CIMP), the prognostically unfavorable mesenchymal subgroup (associating NF1 mutations/loss), and the less prognostically robust classical (associating gain of chromosome 7 and loss of chromosome 10, EGFR amplification/mutations, CDKN2A/B homozygous loss) (this subgroup also associated a unique methylation signature, RTK-II), and neural subgroups (associating EGFR amplification). Importantly, these expression profiles do not hold in the pediatric population. Whereas IDH-mutant GB usually associates TP53/ATRX mutations, IDH-wild-type GB associates TERT promoter mutations.

Although indistinguishable on histology from adult GB, pediatric GB is a totally different entity from a molecular standpoint. Pediatric/young adult GB have H3F3A and HIST1H3B/C mutations. The histone H3 K27M mutation is common in the midline and is associated with a particularly poor outcome and a unique methylation profile. The histone H3 G34R/V mutations are common in the cerebral hemispheres. Histone H3 and IDH mutations are mutually exclusive but histone H3 mutations frequently associate TP53 mutations. The histone H3 G34R/V mutations associate a hypomethylator DNA profile (also known as CpG hypomethylator phenotype - CHOP) and specific gene expression profiles. Pediatric/young adult hemispheric GB usually has TP53 mutations, NTRK1/2/3 fusions, SETD2 mutations, CDKN2A deletions, and PDGFRA alterations. SETD2 mutations are mutually exclusive with histone H3 G34R/V mutations. ACVR1 mutations associate histone H3 K27M mutations in diffuse infiltrative pontine glioma. PDGFRA alterations are associated with a unique methylation signature (RTK-I). PDGFRA, MYC, and MYCN amplifications are more common in pediatric GB compared to adults.

Of most importance from a clinical perspective for both adults and children is the determination of the MGMT promoter methylation status. A methylated MGMT promoter status is encountered in ~75% of the G-CIMP GB (proneural) and ~50% of the pediatric GB patients. It is predictive of response to alkylating agent (i.e. temozolomide) chemotherapy and radiotherapy. MGMT promoter methylation testing is currently performed at Michigan Medicine, Ann Arbor, MI using methylation-specific PCR with a turn-around time of 5-7 business days.

Continued—

Adult GB usually has significantly more copy number alterations compared to pediatric GB. Pediatric GB sometimes lacks any detectable copy number alterations. Common copy number alterations in GB are -6q, +7, -9p, -10, -13q, -14q, +19, +20, -22q. Gain of 1q is more common in pediatric GB. Current molecular testing for copy number aberrations at MUSC is performed by SNP-array. This assay uses more than 800k markers to provide information on the copy number status of the entire genome. Using this assay an overall genomic signature can be obtained and subclassification in the 4 TCGA subgroups defined above can be made most of the times.

Chromothripsis is very common in GB. A GB hypermutator phenotype is caused by inactivating mutations in the DNA mismatch repair genes and usually is induced after treatment and is common at tumor recurrence sometimes inducing drug resistance.

Nevertheless GB is a very complex entity both from a diagnostic/molecular and a clinical perspective. Whereas recent advances expanded our knowledge on this aggressive entity many puzzles still need to be solved in order to significantly improve patient survival, conquer treatment resistance, and improve overall GB-related morbidity. At MUSC our group of neuropathologists and molecular pathologists offer the highest standard of care currently available for GB diagnostics. We work closely with our neurosurgical and neuro-oncology teams to provide exceptional patient care. In parallel, our active translational and basic science research laboratories focused on brain cancer work tirelessly on further elucidating the hidden faces of this menacing entity.

Selected references:

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2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Ellison DW, Figarella-Branger D et al. WHO Classification of Tumours of the Central Nervous System, 4th revised edn. IARC: Lyon (France), 2016.
3. Johnson BE, Mazon T, Hong C, Barnes M, Aihara K, McLean CY et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. *Science* 2014; 343: 189-193.
4. Nounshmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. *Cancer cell* 2010; 17: 510-522.
5. Sturm D, Witt H, Hovestadt V, Khuong-Quang DA, Jones DT, Konermann C et al. Hotspot mutations in H3F3A and IDH1 define distinct epigenetic and biological subgroups of glioblastoma. *Cancer cell* 2012; 22: 425-437.
6. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer cell* 2010; 17: 98-110.

### **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.

**[www.musc.edu/pathology](http://www.musc.edu/pathology)**