



UTHealth™

Medical School

The University of Texas  
Health Science Center at Houston



**2014 SUMMER RESEARCH PROGRAM  
STUDENT ABSTRACTS**

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# Preface

The University of Texas Medical School at Houston (UTMSH) Summer Research Program provides intensive, hands-on laboratory research training for MS-1 medical students and undergraduate college students under the direct supervision of experienced faculty researchers and educators. These faculty members' enthusiasm for scientific discovery and commitment to teaching is vital for a successful training program. It is these dedicated scientists who organize the research projects to be conducted by the students.

The trainee's role in the laboratory is to participate to the fullest extent of her/his ability in the research project being performed. This involves carrying out the technical aspects of experimental analysis, interpreting data and summarizing results. The results are presented as an abstract and are written in the trainees' own words that convey an impressive degree of understanding of the complex projects in which they were involved.

To date, more than 1,800 medical, college, and international medical students have gained research experience through the UTMSH Summer Research Program. Past trainees have advanced to pursue research careers in the biomedical sciences, as well as gain an appreciation of the relationship between basic and clinical research and clinical practice.

UTMSH student research training is supported by a grant from the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and/or by financial support from the Dean and the departments and faculty of the medical school and School of Dentistry.

Biomedical science education remains a vital and integral part of our nation's interests. The UTMSH Summer Research Program, and the dedication of our faculty and administration exemplify the institution's commitment to training and educating the future leaders in our biomedical scientific communities.



Gary C. Rosenfeld, Ph.D.  
Director, Summer Research Program  
Assistant Dean for Educational Programs

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# Acknowledgements

This publication marks the completion of the twenty-fifth year of The University of Texas Medical School at Houston (UTMSH) Summer Research Program. The longevity and success of the program are rooted in the overwhelming support received from the deans, faculty, staff and students of the medical school.

Indicative of this support is the administrative assistance and financial support for the Program's college and medical students provided by UTMSH. Sincere appreciation is expressed to Dean Giuseppe Colasurdo M.D. and Patricia M. Butler, M.D., Associate Dean, Office of Educational Programs who continue to ensure the yearly success of the Summer Research Program.

Major financial assistance for medical students has also been provided through short term research grants by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; 5 T32 DK007676) and the National Institute for Neurological Disorders and Stroke (NINDS; 5 T35 NS064931).

Negotiated cooperative agreements with several international medical schools have been set up to offer tailored research programs at UTMSH for selected foreign medical students who interact fully with the other students in the Summer Research Program.

The success of the Summer Research Program depends primarily on the faculty who volunteer to mentor the trainees. These dedicated educators organize and guide the research projects that includes for each student data analysis, preparation of an abstract and public presentation of results. Our sincere appreciation to all faculty mentors.

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# Lab Research Ownership

## *Publication and/or Disclosure*

*Each student participating in this program is required to read, agree to, and sign this disclosure form. The original signed copy is on file in the Summer Research Program office; the student and their faculty mentors are each furnished with a copy.*

“In reference to the laboratory research you will perform this coming summer through The University of Texas Medical School at Houston’s Summer Research Program, you are required to comply with the standard restrictions regarding participation in the Summer Research Program:

“All of your laboratory research is *CONFIDENTIAL* and although your abstract will be available through our website, you cannot independently disclose or publish any research findings or data in any form (including at meetings or conferences) without the express prior written approval of The University of Texas Medical School at Houston. If you wish to submit your abstract to any third party, you must first contact your faculty mentor no less than three (3) weeks prior to any deadlines in order to obtain the necessary written approvals.

“Because your research was generated from ideas and funds that originated with your faculty mentor and The University of Texas Medical School at Houston, ownership of any data generated by you during the Summer Research Program belongs to The University of Texas Medical School at Houston or the Principle Investigator (PI).”

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# Medical Students

## **ABSTRACT**

### **The Effect of Body Mass Index on the Types and Frequency of Cervical Spine Injury**

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*The University of Texas at Houston Medical School*

*Class of 2017*

Sponsored by: Susanna C. Spence, MD, Department of Diagnostic and Interventional Radiology

Supported by: Susanna C. Spence, MD, Department of Diagnostic and Interventional Radiology; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Cervical spine, injury mechanism, patient risk factors

Cervical spine injuries are considered high risk and are prevalent in trauma centers nationwide occurring in approximately 3.5% of all trauma patients. Because of their relatively common occurrence and the gravity of associated complications, it is not unusual that cervical spine injuries have been the subject of previous studies analyzing high risk patient groups and related mechanism of injury. However, the relationship between body mass index (BMI) and the risk of sustaining a cervical spine injury has been largely understudied. The primary objective of this study is to evaluate the frequency and types of cervical spine injuries at Memorial Hermann Hospital in relation to mechanism of injury and patient BMI. By determining the frequency of cervical spine injuries in relation to mechanism of injury and patient BMI, we hope to help clinicians better diagnose and treat cervical spine injuries. Approximately 8,000 cases of all ages, both genders, and all general health statuses arriving at Memorial Hermann ER or Memorial Hermann Children's ER for initial trauma workup from January 2013 to December 2013 will be reviewed. Patients were excluded from the study if the cervical spine CT scan was a follow-up of a previous injury or if the patient's examination was a repeat of a CT scan already in the study. As of October 3, 2014, 1,693 cervical spine CT scans without contrast were reviewed and classified based on 1) Positive/negative injury; 2) Injury type; 3) Injury mechanism; 4) Patient age, gender, ethnicity, BMI; and 5) Additional factors that predispose the patient to injury. Of the 1,693 cases reviewed, 147 patients were found to have positive cervical spine CT resulting in an 8.682% positive cervical spine injury rate. Regarding patient BMI, normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), and obese (BMI >29.9) patients had a positive injury rate of 10.9%, 12.4%, and 7.1% respectively. Of the three BMI classes mentioned, motor vehicle collisions (MVCs) were responsible for 52.985% of the observed cervical spine injuries. However, within the normal weight, overweight, and obese classes, MVCs accounted for 51.020%, 63.793%, and 33.333% of the positive injury cases respectively. Lastly, within the rollover subset of MVCs, 10.000% of obese patients suffered an injury while 24.490% of normal weight, and 26.829% of overweight patients sustained a cervical spine injury. Although data collection is ongoing and the final results may differ slightly, these preliminary findings reveal some interesting relationships between the incidence of cervical spine injury and mechanism of injury/patient BMI. As data collection continues, these relationships along with others will be further analyzed.

## **ABSTRACT**

### **An Examination of Ubiquilin-2's Molecular Chaperone Ability on Model Client Proteins**

AZAEEL ARIZPE

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*Class of 2017*

Sponsored by: Darren F. Boehning, Ph.D, Department of Biochemistry and Molecular Biology

Supported by: The University of Texas at Houston Medical School – Office of Educational Programs

Key Words: ALS, Ubiquilin 2, Molecular Chaperones

**Background:** Amyotrophic Lateral Sclerosis (ALS) is a debilitating motor neuron disease that affects tens of thousands of people worldwide. The hallmark of ALS is neuronal cell death in the spinal cord and brain leading to paralysis and death. A recent study has indentified mutations in the X-linked gene UBQLN2 gene, ubiquilin-2, to be associated with familial ALS. The purpose of this study is to examine UBQLN2's ability to prevent aggregation.

**Methods:** Four six well plates of HeLa cells were transfected using transfection reagent lipfectamine 2000 with APP-GFP DNA, which is known to form aggregates. Two of each of the wells of each plate were also transfected with UBQLN1 DNA as a control since UBQLN1 is a known molecular chaperone. Two other wells of each plate were transfected with UBQLN2 to test molecular chaperone activity. The other two wells were transfected with APP-GFP and filler DNA. These plates where then allowed to incubate for 48 hours. Each cover slip was examined using fluorescence microscopy. Each cell that fluoresced was placed into one of three categories: Normal cells (no aggregates), one aggresome, and multiple aggregates.

**Results:** There was poor transfection efficiency with transfection reagent lipofectamine 2000, we had few cells showing fluorescence. Therefore, there was no statistical significant difference between the three exposures.

**Discussion:** Poor transfection could be due to lipofectamine 2000 or the amount of DNA used. The methods will be repeated using a new transfection reagent (lipofectamine 3000) and different DNA concentrations in order to maximize transfection efficiency.



## **ABSTRACT**

### **Nondisplaced Skull Fractures in Children: Is Hospital Admission always Necessary?**

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Sponsored by: David I. Sandberg, MD, Department of Pediatric Surgery, Department of Neurological Surgery

Supported by: National Institute of Neurological Disorders and Stroke, 5T35NS064931-05

Key Words: Head injury; pediatric; nondisplaced skull fracture; hospital admission; trauma

**INTRODUCTION:** Linear nondisplaced skull fractures (NDSFx) require no neurosurgical repair or intervention. This review evaluates the outcomes and clinical management of patients with isolated NDSFxs.

**METHODS:** A retrospective database was created with the complete profiles of pediatric patients admitted with NDSFxs from January 1, 2009 to December 31, 2013 at Children's Memorial Hermann Hospital (CMHH). Exclusion criteria consisted of patients with intracranial bleeding, two or more NDSFxs, pneumocephalus, and comminuted or open skull fractures.

**RESULTS:** 327 patients met inclusion criteria: 83% (272) were admitted to the hospital and 17% (55) were discharged from the Emergency department. Means of arrival: 85% (279) by ambulance, 11% (36) by car, and 4% (12) by flight. 78% (256) were transferred from another institution. Length of hospital stay ranged from several hours to as much as 16 days. The median hospital stay was 1 day. 83% (226) of the admitted patients spent a day or less. Of the patients that required more than 24 hours of admission, 52% (24) of extended admissions were due to CPS involvement and 20% (10) were due to patients having multiple injuries. 14% (45) had altered mental status or loss of consciousness by history. No patient had any neurological deficits or CNS findings on exam, and none required neurosurgical intervention. Less than 16% (50) followed up in clinic upon discharge.

**CONCLUSION:** Many patients with skull fractures are transferred to trauma centers for a higher level of care. As patients with NDSFxs need no neurosurgical intervention, such transfers and admissions are costly and often unnecessary.

## **ABSTRACT**

### **Risk Classification Model for Averse Clinical Outcomes in Childhood Bacterial Meningitis**

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Sponsored by: Rodrigo Hasbun, MD, Department of Infectious Disease

Supported by: Rodrigo Hasbun, MD, Department of Infectious Disease

Key Words: Childhood, Meningitis, Risks, Model

Childhood bacterial meningitis is a disease that can easily be misdiagnosed or mistreated leading to adverse clinical outcomes for patients. Although a risk classification model currently exists for adult bacterial meningitis, there is no risk classification model for children with bacterial meningitis at this time. The purpose of this study was to create a database in order to derive and validate a risk classification model for childhood bacterial meningitis. This risk classification model would allow physicians to quickly evaluate a child with suspected bacterial meningitis and determine the chances that they would develop an adverse clinical outcome. Our study population in this retrospective study was collected from several different hospitals. The criteria for inclusion were that the patient (1) was under 18 years of age, (2) had bacterial meningitis confirmed by gram stain or CSF culture, (3) presented to one of the participating hospitals after 1985. Specifically over this summer I collected data from Children's Memorial Hermann Hospital electronic medical records. All patient identifiable information is secured in accordance with HIPPA. The data collected included demographics, presenting symptoms, disease progression, and how the patient was treated with antibiotics or steroids. Each patient was also designated as having or not having an adverse clinical outcome. An adverse clinical outcome in this study was defined as death, hearing loss according to an audiogram, or neurosequelae. Once the database is completed we will use statistical analysis to determine which factors have a positive correlation with adverse clinical outcomes. This information will then allow us to create a risk classification model. We believe that several factors will correlate with adverse clinical outcomes which will provide helpful information to clinicians with patients in the future. As of 8/1/2014 data collection is ongoing and therefore no results are available at this time.

## ABSTRACT

### Fast Method for Quantitative Magnetization Transfer Imaging

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Supported by: The University of Texas at Houston Medical School – Office of The Dean

Key Words: Quantitative magnetization transfer, balanced steady-state free precession, signal-to-noise ratio, magnetic resonance imaging

Quantitative magnetization transfer (qMT) imaging provides critical information about the state of myelin in the human brain. A major application of this technique is to reliably quantify and monitor demyelination in patients with multiple sclerosis and other demyelinating diseases. However, despite the clinical utility of the parameters generated by qMT imaging, this technique has not yet seen widespread clinical use. This is primarily due to the lengthy scan times (usually in excess of an hour) required to generate the quantitative data using traditional protocols. In this study, we investigated the use of balanced steady-state free precession (bSSFP; a fast MRI sequence) to obtain the qMT parameters:  $T_{2f}$  ( $T_2$  relaxation time of the free pool),  $F$  (fraction of bound to unbound protons), and  $k_f$  (rate constant of magnetization transfer) that characterize the state of myelin. We acquired data on two healthy subjects using a Phillips 3T scanner and performed post-scan computation and analysis of the data using software written using MATLAB. The qMT values that were obtained were quite different from values that had been previously reported in the literature. Quantities that could have a significant effect on the qMT values include signal-to-noise ratio (SNR) and radio frequency field ( $B_1$ ) of the scanner. In order to better understand the effects of SNR on the qMT parameters, we performed Monte Carlo simulations. These simulations demonstrated that the qMT parameters are quite sensitive to low SNR, particularly the pool fraction ( $F$ ) and rate constant ( $k_f$ ). Work is underway to increase the SNR by averaging multiple acquisitions at each point in the protocol and by increasing slice thickness. Once the protocol is optimized and acceptable values are obtained for the qMT parameters, more healthy volunteers will be scanned to confirm the reliability and reproducibility of this method.

## **ABSTRACT**

### **Effects of Extended Release Methylphenidate on Selective Attention in Children with Autism Spectrum Disorders (ASD) and ADHD Symptomatology**

*ALIXANDRA BAYCROFT    The University of Texas at Houston Medical School    Class of 2017*

Sponsored by: Deborah Pearson, PhD, Department of Psychiatry and Behavioral Sciences

Supported by: The Bernard Saltzberg Summer Research Fellowship, Department of Psychiatry and Behavioral Sciences

Key Words: Autism, ADHD, Methylphenidate, Attention

A significant number of children (14-75%) diagnosed with Autism Spectrum Disorder (ASD) also display symptoms of inattention, hyperactivity, and impulsivity that warrant a diagnosis of ADHD. The recently released DSM-V allows for a diagnosis of ADHD in patients with ASD, and an estimated 58% of children with these diagnoses are being treated with psychotropic medication. The purpose of this study was to determine the effects of four doses of extended release methylphenidate (ER-MPH) on selective attention in children with ASD and symptoms of ADHD. Another objective of this study was to determine whether the resulting dose-response curve was linear (indicating gains in attention with increased ER-MPH dosages) or curvilinear (indicating initial gains in attention with ER-MPH followed by lesser improvements or declines). Study participants met both DSM-IV-TR criteria for ASD and DSM-IV criteria for ADHD. The first week of the trial was single-blind with each child receiving placebo. During the following three weeks, each child received one week each of three doses (low, medium, and high) based on body weight. At the end of each week, selective attention was assessed using three different measures: a speeded classification task, a span of apprehension task, and a dichotic listening task. Performance on the speeded classification task ( $p < 0.005$ ), span of apprehension task ( $p < 0.002$ ), and dichotic listening task ( $p < 0.001$ ) all improved in a linear fashion with increasing doses of ER-MPH. These findings suggest that ER-MPH treatment improves selective attention in children with ASD and symptoms of ADHD.

## ABSTRACT

### Aortic Remodeling after TEVAR for Acute Complicated Type B Aortic Dissection

RYAN BISHOP

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*Class of 2017*

Sponsored by: Ali Azizzadeh, MD, Department of Cardiothoracic and Vascular Surgery

Supported by: The University of Texas at Houston Medical School – Office of the Dean

Key Words: Aortic dissection, aortic remodeling, TEVAR, stent-graft

**Background:** Thoracic endovascular aortic repair (TEVAR) is a treatment option for patients with acute complicated type B aortic dissection (ACTBAD). The optimal extent of aortic coverage during TEVAR is not well defined. Our current practice involves coverage of the proximal entry tear with a single device. The purpose of this study was to evaluate aortic remodeling after TEVAR for ACTBAD.

**Methods:** We reviewed TEVAR patients with ACTBAD between 2006-2014. The diameter, total aortic area, true lumen (TL), and false lumen (FL) were measured at six locations (1. left subclavian, 2. pulmonary artery, 3. left atrium, 4. celiac, 5. lower renal artery, 6. infrarenal aorta). A specialized radiologist obtained measurements using 3D software (TeraRecon, Fostercity, CA). The FL was classified as patent, partially thrombosed, or thrombosed. Differences in diameter and area were computed and transformed to relative frequency (percent change from baseline). Percent change was analyzed in its native distribution and as distribution-free rank variables. Data were analyzed by linear multilevel model, using MIXED procedure in SAS 9.3 (SAS Institute Inc., Cary, NC).

**Results:** During the study period, 44 patients (median age of 64.5, 73% male) underwent TEVAR for ACTBAD. The 30 mortality, stroke, and paraplegia was (20.5%, 4.55%, 18.2%) respectively. Seventeen patients who had complete imaging datasets were included in the study. The mean extent of aortic coverage was 19.8 cm. Total aortic diameter was not changed by TEVAR at any location ( $p=0.78$ ). TL diameter and area were increased by 100% and 150%, respectively, at locations 2 and 3 ( $p<0.005$ ). FL diameter and area were reduced by 50% percent each at locations 1 and 3 ( $p<0.04$ ). Luminal diameters beyond the stent-graft were unchanged. The FL was thrombosed over the treated segment in 70% while the FL was patent in the untreated segment of the aorta in 100%. The median time for follow-up imaging was 36 days (IQR 17-48).

**Conclusion:** Aortic remodeling occurred as expected in the segments covered by the stent-graft, but distal segments were unchanged. This raises the question of whether exclusion of the proximal entry tear alone is sufficient, or whether extension of coverage is necessary. Long-term studies are indicated to determine the optimal length of coverage.

## ABSTRACT

### Suture, Synthetic, or Biologic Mesh? A Multi-center Comparison of Contaminated Ventral Hernia Repair

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Sponsored by: Lillian S Kao, MD, MS, Mike K Liang, MD, Department of Surgery

Supported by: The University of Texas at Houston Medical School – Office of Educational Programs

Key Words: Ventral hernia repair, mesh, suture, contamination

**Background:** While there is little controversy regarding the improved outcomes associated with mesh use in uncomplicated ventral hernia repair (VHR), data is lacking to support the choice between suture, light-weight synthetic mesh, or biologic mesh in contaminated VHR. We hypothesize that in contaminated VHR, suture repair is associated with a lower rate of surgical site infection (SSI) and a higher rate of hernia recurrence compared to light-weight synthetic and biologic mesh.

**Methods:** We reviewed a multi-center, retrospective database of all open VHR performed at seven institutions between 2010-2011. All patients with a Centers for Disease Control and Prevention (CDC) wound classification of II-III were included. The primary outcome was SSI as defined by the CDC. The secondary outcome was hernia recurrence (assessed clinically and radiographically). Multivariable analysis using stepwise regression was performed including variables selected a priori (ASA, BMI, current smoking, acute, primary versus incisional hernia, prior hernia repair, wound class II or III, fascial release, fascial closure, repair technique-suture or light-weight mesh or biologic mesh, and follow-up duration). Inverse probability weighting (which corrects for selection bias and missing data) was also performed adjusting for the listed variables as well as defect size and institution.

**Results:** 204 contaminated VHRs were reviewed for a median follow-up of 12.8 months (range 1-49); there were 72(35%) suture, 66(32%) light-weight synthetic mesh, and 66(32%) biologic mesh repairs. On univariate analysis, there were differences in the three groups including institution, ASA score, prior hernia repair, wound class, size, and fascial release. The unadjusted outcomes of SSI (9.7%,18.2%,12.1%; $p=0.32$ ) and recurrence (26.4%,13.6%,19.7%; $p=0.17$ ) were not statistically different between the groups.

On multivariable analysis, repair technique was not associated with SSI but did impact recurrence (Table). Using inverse probability weighting, there was no difference in SSI between the study groups. The rate of recurrence for suture repair was 38.6%; synthetic mesh reduced the recurrence rate to 8.8% (CI2.5-15.2%) while biologic mesh had no impact (31.8%,CI9.9%-53.7%).

**Conclusions:** In contaminated ventral hernias, mesh repair (lightweight synthetic or biologic) compared to suture repair, does not increase the surgical site infection rate but may decrease the recurrence rate. While we attempted to risk-adjust our outcomes, this study is limited by selection bias and its retrospective nature. In the absence of higher level data, the results of this multi-center study suggest that light-weight synthetic mesh may be a safe choice in contaminated ventral hernia repair.

## ABSTRACT

### Evaluation of StO<sub>2</sub> Tissue Perfusion Monitoring as a Tool to Predict the need for Life Saving Interventions in Trauma Patients

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Sponsored by: Laura J. Moore, MD, FACS, Department of Surgery

Supported by: Laura J. Moore, MD, FACS, Department of Surgery, Center for Translational Injury Research (CeTIR); University of Texas at Houston Medical School – Office of the Dean

Key Words: Trauma, hemorrhage, perfusion, StO<sub>2</sub>, military medicine

Hemorrhagic shock and hemodynamic instability are difficult conditions to assess in trauma patients due to the human body's unique compensation mechanisms which can preserve widely-used vital signs such as blood pressure, pulse, and GCS. Earlier diagnosis of hemorrhagic shock universally increases survival rates due to increased time to implement Life Saving Interventions (LSI) such as blood transfusions, procedures and medications. Decreased peripheral tissue perfusion, analyzed by StO<sub>2</sub> monitoring, is one of the compensatory mechanisms that the body uses to maintain hemodynamic stability; shunting blood away from non-vital tissues such as peripheral muscle can preserve the functionality of the life-sustaining core organs. In addition to the potential to predict the need for LSIs, allowing more time for interventions, StO<sub>2</sub> monitoring can enable providers to gauge the body's physiologic responses to help make decisions on the need for additional measures. In military theatres, which often lack expensive prehospital monitoring devices, the basic delineation of "sick" and "nonsick" patients often unintentionally ignores a subset of patients who present with normal vital signs, yet who display hidden, microcirculatory changes resulting from hemorrhage. StO<sub>2</sub> monitoring can allow military healthcare providers an additional tool to assess the hemodynamic status of critically injured soldiers, and assist in making decisions of interventions and appropriate trauma center destination under extreme time restraints in dangerous environments. If proven successful, StO<sub>2</sub> monitors could be implemented on medical helicopters in the United States and abroad to allow quicker implementation of LSIs, eliminate unnecessary blood transfusions, and cut costs by preventing resource shortages.

**Study Population:** Level 1 trauma activation patients without transfer from another hospital are enrolled. Patients with >30% burns or bilateral upper extremity fractures are excluded. StO<sub>2</sub> readings are recorded every 5 minutes in the trauma unit and immediately after each LSI, and lab values and other information are recorded from EMR. All patient identifiers are secured in accordance with IRB and HIPAA protocols.

**Hypothesis:** Trends in StO<sub>2</sub> readings can be used to predict the need for LSIs.

**Results:** As of 8/1/14, data collection is ongoing, therefore no results are available at this time.

## ABSTRACT

### Surgical Antibiotic Prophylaxis Requires More Than Operating Room Interventions

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*Class of 2017*

Sponsored by: Kuojen Tsao, MD, Department of Pediatric Surgery

Supported by: Kuojen Tsao, MD, Department of Pediatric Surgery

Key Words: Prophylactic antibiotics adherence; antibiotic prophylaxis guidelines; pre-incisional surgical safety checklist, interventions

**Introduction:** Proper prophylactic antibiotic administration includes adherence to all components: appropriate administration, type, dose, timing, and redosing. We previously demonstrated that 52% of operations suffered from at least one incorrect component of proper administration. In response, a multiphase, multifaceted prophylactic antibiotic program was created with the hypothesis that overall adherence to prophylactic institutional guidelines would increase.

**Methods:** From 2011-2014, three 10-month interventional periods were conducted which implemented adoption of Surgical Care Improvement Project-based pediatric antibiotic prophylaxis guidelines (2011), integration of checkpoints into the pre-incision surgical safety checklist/creation of a computerized physician order entry module (2012), and role assignment to anesthesiology for administration (2013); audit/feedback was performed throughout. Following each period, an 8-week direct-observational assessment was performed. Perioperative factors that may influence guideline adherence including wound class, surgical specialty, patient weight, and anesthesia provider were analyzed. Spearman's rank correlation and chi-squared analysis were performed,  $p < 0.05$  was considered significant.

**Results:** 1,052 operations were observed. Prophylactic antibiotics were indicated in 629 (60%) in which 625 (99%) received them. Conversely, antibiotics were not indicated in 421 cases (40%) in which 358 (85%) did not receive antibiotics. For cases requiring antibiotics, adherence to the four administration components remained unchanged (54% to 55%,  $p = 0.99$ ). Only redosing significantly improved (7% to 53%,  $p = 0.02$ ), whereas correct type declined (98% to 70%,  $p < 0.01$ , Table). This decline was mostly attributed to two surgeons who were unaware of updated 2013 institutional guidelines, but utilized an acceptable antibiotic. Otherwise, correct type and overall adherence in 2014 would have been 89% and 72%, respectively. Adherence to guidelines did not differ significantly based on ASA class, surgical specialty, patient weight, anesthesia provider, or surgical wound class (all  $p > 0.05$ ).

**Conclusions:** Despite multiple interventions to improve antibiotic prophylaxis, overall adherence did not significantly increase. Although most interventions were directed at point of administration in the operating room, proper dissemination of institutional guidelines remains a challenge. Future strategies will require additional educational initiatives as well as a perioperative approach towards process standardization to improve adherence to antibiotic prophylaxis administration.



## ABSTRACT

### C-fos Induction by NPY in the Paraventricular Hypothalamic Nucleus is Indirect

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Key Words: NPY, C-fos, feeding, PVN, insulin

**Background:** It is well established that activation of paraventricular hypothalamic (PVN) neurons inhibits feeding whereas silencing of these neurons increases feeding. However, neuropeptide Y (NPY), a potent orexigenic peptide, induces abundant expression of C-fos, a marker of acute neuronal activation, in the PVN. The reason for the apparent discordant hyperphagia and C-fos induction by NPY is unknown. Previous studies suggest that NPY decreases GABA-mediated inhibitory postsynaptic currents on PVN neurons and that NPY increases blood insulin concentration, which is able to induce C-fos in the PVN. To evaluate the contrasting phenomenon of concurrent C-fos induction in PVH and feeding promotion by NPY, the present study aimed to examine whether the NPY effects on feeding and C-fos in the PVN are mediated indirectly through GABA-A receptors or insulin.

**Methods:** Mice with PVN specific genetic disruption of the GABA-A receptor (n=5), wild-type mice with streptozotocin (STZ)-induced diabetes (n=6) or wild-type mice (n=9) received intracerebroventricular injections of NPY (2  $\mu$ L) or saline, monitored for 2-hour food intake, and then were perfusion-fixed with paraformaldehyde. Brains were sectioned and processed for C-fos using Calbiochem PC38 Anti-C-fos rabbit antibody. Three sections with evident PVN structure from each mouse were examined with fluorescence microscopy. Food intake and average C-fos expression in PVN for each group were compared.

**Results:** NPY-injected GABA-A- $\gamma$ 2 knock-out mice exhibited lower food intake and less C-fos expression in the PVN compared to NPY-injected controls. The hyperphagic effect of NPY was completely lost in diabetic mice. Compared to NPY-treated control mice, the orexigenic effect of NPY was also reduced in diabetic mice, which was associated with significantly less C-fos in PVN. Interestingly, there appeared to be a positive correlation between NPY-mediated food intake and C-fos expression in the PVN which awaits confirmation through further replication.

**Conclusions:** This study suggests that both GABA-A receptors and insulin (or other factors associated with type 1 diabetes) are required for NPY effects on feeding and C-fos induction in the PVN. Our study shows for the first time that NPY-induced hyperphagia is lost in type 1 diabetes. Correlation between NPY-mediated feeding and C-fos expression suggests that increased PVN neuron activity mediates NPY hyperphagia. Further studies are required to examine the reasons for the discordance between feeding promotion by NPY-induced C-fos in PVN and feeding promotion by direct PVN neuron inhibition.

# ABSTRACT

## Interference with Cell Membrane Adaptation and its Influence on Daptomycin Resistance in *Enterococcus faecium*

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Sponsored by: Cesar A. Arias, MD, PhD, Internal Medicine – Infectious Diseases

Supported by: Cesar A. Arias, MD, PhD, Internal Medicine – Infectious Diseases; The  
University of Texas at Houston Medical School – Office of the Dean

Key Words: *Enterococcus faecium*, Daptomycin, adaptation, VRE

**Introduction:** Vancomycin-resistant *Enterococcus faecium* (Efm) are among the leading causes of nosocomial infections. Daptomycin (DAP), a lipopeptide antibiotic that targets the bacterial cell membrane, is currently the only bactericidal antibiotic available against VRE. However, resistance to DAP is rapidly emerging in multidrug resistant (MDR) *E. faecium* (Efm) and other VRE during treatment. Therefore, new therapies are urgently needed. LiaFSR is a regulatory system involved in the bacterial cell membrane response to antimicrobials that target the cell envelope and substitutions in the members of this system have been associated with development of DAP resistance. In some Efm strains, mutations in another cell envelope regulatory system (designated YycFG and accessory proteins) appears to mediate DAP resistance independent of changes in LiaFSR. Thus, the goal of this study was to determine whether deletion of the gene encoding the response regulator LiaR influence the DAP phenotype in an Efm strain harboring substitutions in YycFG.

**Methods:** Efm HOU515 exhibits a DAP MIC of 3 µg/ml and harbors a predicted A414T substitution in the putative histidine kinase YycG. In order to generate a non-polar *liaR* deletion, flanking regions of the gene were amplified and cloned in pHOU1. The recombinant pHOU1 derivatives were electroporated into *E. faecalis* CK111. In order to introduce the plasmids into Efm HOU515, conjugation experiments were performed using *E. faecalis* CK111 as the donor and a fusidic acid derivative of Efm HOU515 as recipients. Second event recombinants (carrying the deletion) were isolated in the presence of p-Chl-phenyl-alanine. Characterization of the mutant was carried out by using pulsed field gel electrophoresis (PFGE) and performing a growth curve in brain-heart infusion broth. Genetic sequencing was done to confirm the *liaR* gene deletion. The MIC of DAP was also evaluated by Etest on Mueller-Hinton agar.

**Results:** A *liaR* mutant was obtained (Efm HOU515<sub>ΔLiaR</sub>) which displayed a ca. 64-fold lower DAP MIC (0.047 µg/ml) compared to the original strain (3 µg/ml). Efm HOU515<sub>ΔLiaR</sub> did not have any growth defects when compared to the fusidic acid derivative of Efm HOU515. In addition, by PFGE the DNA profile was identical compared to those of the corresponding parental strains Efm HOU515 and Efm HOU515 FA.

**Conclusions:** LiaR is critical to the development of daptomycin resistance in some *E. faecium* isolates, regardless of pre-existing mutations in other cell membrane altering pathways.

# ABSTRACT

## Individual Differences in Eye Movements During Speech Perception

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Sponsored by: Michael S. Beauchamp, PhD., Department of Neurobiology and Anatomy

Supported by: National Institute of Neurological Disorders and Stroke, 5T35NS064931-05

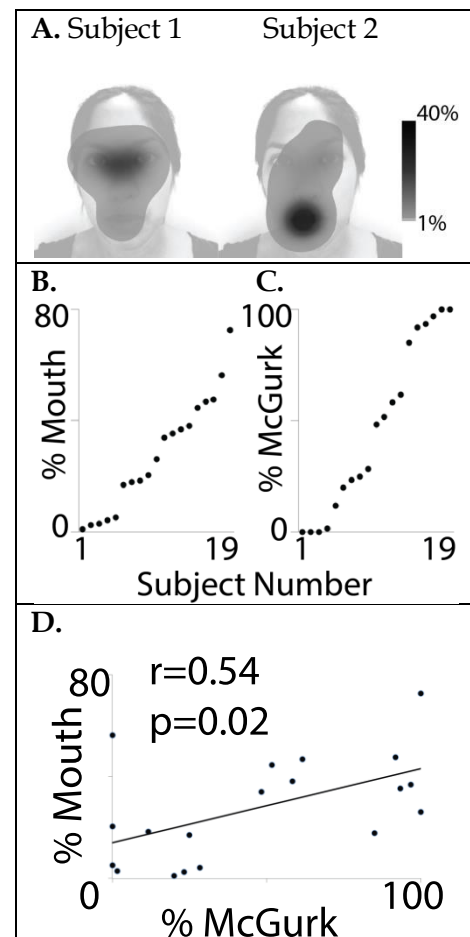
Key Words: eye movements, speech perception, individual differences

**Introduction:** Understanding speech is one of our most important cognitive abilities and makes use of both the auditory and visual modalities. A demonstration of this multisensory integration is an illusion known as the McGurk effect. When presented with some combinations of auditory and visual syllables, subjects perceive neither the auditory nor the visual syllable but a third, completely different syllable. However, some subjects do not experience this illusion and only report the auditory syllable, suggesting that they do not make use of visual speech information.

**Methods:** 19 healthy adults (11 female, mean age 24) viewed two-second videos of a person saying a syllable (30 repetitions of 4 congruent syllables and 2 McGurk syllables) and reported their percept. Subjects' eye movements were recorded using an Eyelink 1000 Plus (SR Research, Inc.) infrared eye tracker. The amount of time subjects spent fixating the eyes and mouth of the talker were measured.

**Results:** There was large variability in the amount of time individuals spent fixating the mouth and eyes of the speaker. Some subjects looked mostly at the eyes, while others looked mostly at the mouth (fig. A, background is a frame from the video, overlay shows fixation duration at each location). Across subjects, mouth fixation time ranged from 0-72% (fig. B). There was also large variability in subjects' perception of the McGurk effect, ranging from 0-100% (fig. C). The amount of time spent looking at the mouth correlated with susceptibility to the McGurk effect (fig. D,  $r = 0.54$ ,  $p = 0.02$ ).

**Conclusions:** The study found that individuals utilize different eye movement patterns to understand audiovisual speech. The McGurk effect requires the observer to use visual cues; individuals who spend more time fixating the mouth of the talker were more likely to perceive the McGurk effect,



implying that they are more influenced by the visual component of speech. Millions of Americans suffer from language impairments due to hearing loss, stroke, and other causes. If looking at the mouth increases the influence of visual speech, then training eye movements in these patients could improve speech comprehension.

## ABSTRACT

### *Aspergillus fumigatus* as an Inducer of Chronic Rhinosinusitis with Nasal Polyps

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Supported by: Amber Luong, MD, PhD Department of Otorhinolaryngology- Head and Neck Surgery; The University of Texas at Houston Medical School – Office of the Dean

Key Words: CRSwNP, *Aspergillus fumigatus*, Protease

**Background:** Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic inflammatory disease affecting the paranasal sinus mucosa, categorized clinically by the presence of nasal polyps and a Th2 inflammatory response. *Aspergillus fumigatus* has been proposed as a possible etiology for the inflammation associated with CRSwNP. The molecular mechanisms of the interactions of fungi and the sinonasal mucosa of CRSwNP patients remain unclear. The objective of this study is to determine the specific fungal component of *A. fumigatus* and its corresponding pattern recognition receptor (PRR) expressed on sinonasal epithelial cells responsible for inducing a Th2 response in CRSwNP.

**Methods:** Primary human sinonasal epithelial cell cultures from CRSwNP patients were stimulated with various components of *A. fumigatus* extracts including fungal protease, chitin, and scleroglucan, over several time points and concentrations. The gene expression of various PRRs including multiple toll-like receptors and protease activated receptors was measured. Levels of IL-33 mRNA expression after stimulation by whole fungal extract, fungal protease, and PMSF (a protease inhibitor) were then measured using real time PCR.

**Results:** This project is still in progress. Samples from 16 CRSwNP patients have been stimulated and analyzed to date. Preliminary results point to fungal protease as the primary fungal component inducing IL-33 expression. Stimulation with 1 mg/mL fungal protease results in increased expression of IL-33 and combined stimulation with fungal protease and PMSF returns IL-33 expression to baseline. These results with fungal protease mirror IL-33 expression with stimulation of *A. fumigatus* whole cell extract with and without PMSF. Protein levels of IL-33 after stimulation remain to be evaluated by ELISA. Stimulation with fungal protease also results in increased expression of PAR2 and this response can be blocked with addition of PMSF. These results need to be replicated to confirm these findings.

**Conclusions:** No conclusions can be made at this point in the project. Further studies are required to confirm preliminary results.

## **ABSTRACT**

### **Intentional Chemical Contamination Tabletop Exercise**

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Sponsored by: Robert J. Emery, DrPH, CHP, CIH, CBSP, CSP, CHMM, CPP, ARM  
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Supported by: The University of Texas at Houston Medical School – Office of Educational  
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Key Words: Emergency Preparedness, Tabletop Exercise, Terrorism, Chemical  
Contamination

While the Houston metropolitan area maintains clear plans for radiological, biological, and industrial chemical disasters, the need exists for a fully developed non-industrial emergency plan for chemical contamination. Chemical disasters can range in severity, with even minor events possibly overtaxing the medical system. Even if a chemical contamination event is limited to a small number of individuals, large populations might go to the hospital to get examined for symptoms that are not necessarily related to that chemical. This makes it harder for the people who are actually affected to get treatment, and also keeps health professionals from being able to see other unrelated sick and injured patients. As such, there is a need for an exercise that includes considerations of these aspects for the emergency response community.

The National Incident Management System (NIMS) Guidelines were used to construct a Tabletop Exercise (TTX) that simulates an intentional chemical contamination event. The actual exercise will be carried out in January 2015 to facilitate communication within and between departments that would be involved in response efforts. The individuals included in the TTX will consist of public health organizations, private health departments, law enforcement, city officials, safety organizations, media relations representatives and media personnel. Their cooperation and feedback will be used to detect weaknesses in general response protocols and will aid in the development of a specific protocol for intentional chemical contamination.

## **ABSTRACT**

### **Investigation of the Therapeutic Use of Surfactant Protein-A in an Experimental Rat Pup Model of Established Necrotizing Enterocolitis**

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Sponsored by: Joseph L. Alcorn, PhD, Department of Pediatrics

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases,  
2T35DK007676-21A1

Key Words: Inflammation, formula, hypoxia, prematurity

Necrotizing enterocolitis (NEC) is a severe gastrointestinal complication affecting mainly premature infants. The combination of inflammation, hypoxia, inappropriate bacterial colonization and enteral formula feeding all contribute to the pathogenesis of NEC in the immature intestine. Current treatments of established NEC options are often invasive and of limited effect, potentially leading to short bowel syndrome and impaired gut absorption. Thus, there is a need for an effective, non-invasive treatment. We tested an innovative technique of administering surfactant protein-A (SP-A), which has been shown to serve an immunomodulatory role in the lungs and potentially ameliorates pathology in an animal model of NEC. More specifically, we tested the efficacy of SP-A to improve outcomes after a NEC-like pathology had already been established. To accomplish this, we used a rat model of NEC. The gut development of newborn rodents mimics that of a 12-weeks gestation human infant. To induce NEC, we separated pups from dams, administered a restricted calorie diet of infant formula with LPS (lipopolysaccharide) by oral gavage and exposed the pups to hypoxic conditions; all of which contribute to the pathological development of NEC. SP-A (5  $\mu\text{g}/\text{pup}/\text{day}$ ) was mixed with formula and was fed to the pups by oral gavage either at the time of induction of NEC or 1 and 2 days after induction of NEC. Survival, histological evaluation of the distal ileum for NEC and detection of pro-inflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ) by ELISA were determined. We performed four experiments. In our first experiment, pro-inflammatory cytokine levels were lower in the hypoxia-treated pups when compared to the untreated control pups, indicating that the model required modification. Our second trial involved a massive diarrhea outbreak, and the resulting mortality left insufficient pups for analysis. The third test was devoted to re-establishing a reliable model of NEC. The results of the fourth experiment suggested that both day 1- and day 2-administered SP-A result in decreased incidence of NEC and lower IL-1 $\beta$  cytokine levels when compared to the hypoxia-treated controls. While statistical significance of the impact of delayed administration of SP-A to ameliorate NEC pathology requires more experimentation, the results of the study indicate that SP-A can potentially be used to affect the pathogenesis of NEC after it has been established.

## ABSTRACT

### In Vitro Comparison of Skeletal Muscle Decellularization Methods

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Sponsored by: Yong Li, MD, Ph.D., Department of Pediatric Surgery

Supported by: Department of Pediatric Surgery

Key Words: Muscle, Extracellular Matrix, Decellularization, Comparison

Skeletal muscle comprises almost half of the human body's mass and is one of the few tissue types to demonstrate regenerative capabilities. However, once a muscle loses more than 20% of its volume (Turner and Badylak, *Eur Cell Mater*, 2013), termed volumetric muscle loss (VML), the regenerative process becomes tainted by scar tissue formation, resulting in alteration of biomechanical properties and functional deficits. VML is common in the civilian population following trauma, infection, degenerative disease, or tumor ablation and is especially prevalent in the military, where deep soft-tissue wounds were involved in 53% of extremity injuries, the most common battlefield injury during recent U.S. conflicts (Owens et al., *J Orthop Trauma*, 2007). Currently, surgical treatment using autologous muscle grafts is the gold standard but only provides partial functional recovery and is accompanied by high donor-site morbidity. As a result, the application of tissue-engineered constructs has been indicated. The tissue engineering approach involves the decellularization of skeletal muscle to obtain its extracellular matrix (ECM), which can be used as a graft to supplement regeneration. Since the cellular components of the muscle are absent, the likelihood of immune rejection is greatly reduced, eliminating the need for autologous grafts. Moreover, the ECM provides a three-dimensional structure for host cell infiltration, proliferation, and differentiation, allowing for the preservation of complex muscle architecture, vascularization, and innervation. Although the ECM is mostly composed of collagen, bound growth factors and cytokines as well as degraded ECM peptides help augment regeneration by recruiting certain cell types and promoting a constructive immune response. The key to preserving ECM structure and composition rests in the decellularization strategy, but numerous decellularization methods exist for skeletal muscle, and a consensus has not yet been reached. A review of the current literature revealed 8 different decellularization protocols. In order to evaluate the efficacy of each protocol, C2C12 myoblasts were cultured on powdered ECMs obtained using each protocol, and their proliferation and differentiation into myotubes were quantified. The ECMs, derived from gastrocnemius muscles of adult C57BL/6 mice, were lyophilized, powdered, and coated onto a 96-well plate with each row of the plate corresponding to a different decellularization protocol; removal of cells was confirmed by hematoxylin and eosin (H&E) and 4',6-diamidino-2-phenylindole (DAPI) staining of nuclei. C2C12 myoblasts were cultured in the wells using growth medium until they reached 70-80% confluency, after which differentiation medium was used. During the growth period, myoblast proliferation was assessed daily by using BrdU incorporation and averaging the number of fluorescent cells within 10 random fields. During the differentiation period, the



quantity and quality of myotube formation was measured daily by averaging the number of myosin heavy chain (MyHC)-positive myotubes as well as the number of DAPI-stained nuclei within those myotubes within 10 random fields. Protocol efficacy was gauged using this data.

## ABSTRACT

### Utilization of an *ex vivo* Human Placental Perfusion Model to Predict Potential Fetal Exposure to Cisplatin During Pregnancy

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Supported by: Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP, Department of Obstetrics, Gynecology and Reproductive Sciences; The University of Texas at Houston Medical School—Office of the Dean

Key Words: Dual reperfusion, cancer during pregnancy, cisplatin, toxicity, fetal accumulation

Testing the safety of drug use during pregnancy presents a unique challenge – as a result many drugs have not been fully evaluated, and there is no formal guideline for physicians to use when prescribing. The purpose of this research is to provide preliminary information on the safety of the use of the cisplatin, a chemotherapy agent used often for the treatment of cancer during pregnancy. Cancer left untreated in particular can be life threatening to mother and fetus yet majority of chemotherapy agents are known to be toxic to fetal development. However, it is still necessary to control the tumor growth during pregnancy to limit progression of disease. Determining the potential fetal exposure and eventually the renal effect of cisplatin will provide evidence that physicians may find valuable in determining the cancer treatment plan for pregnant patients. In this study human placentas were used in an *ex vivo* single cotyledon, dual reperfusion model, with both an open and a closed component of the experiment. Perfusion of cisplatin was examined at a low (1  $\mu\text{g}/\text{mL}$ ) and high (5  $\mu\text{g}/\text{mL}$ ) concentration. Antipyrine, a compound that is highly diffusible across the placenta, was used as a positive control to compare the perfusion of cisplatin at the varying concentrations. This model can be used to evaluate the permeability of the placental/trophoblastic barrier to cisplatin. This study will help determine the transport fraction, clearance index, and potential for accumulation in fetal tissue. The first value calculated includes the transport fraction and the accumulation of cisplatin – the former via an open system with no recirculation, and the later via a closed circulation. Samples from both fetal and maternal compartments are to be obtained every ten minutes in triplicate for each experiment so that the concentration of cisplatin and antipyrine can be determined. Using this information, the effects of cisplatin drug exposure on fetal tissue development – based on the observed concentrations in the fetal compartment – will help evaluate the current cisplatin usage in clinical management of cancer in the pregnant population. Mean transport fractions for cisplatin at low and high concentrations were  $0.31 \pm 0.03$  and  $0.21$ , respectively. The clearance indexes for cisplatin at the same concentrations were  $1.45 \pm 0.62$  and  $1.04$ , respectively. The highest concentration of cisplatin that crossed placental barrier for the low concentration was  $223.8 \pm 52$   $\text{ng}/\text{mL}$  and the peak cisplatin concentration for the high concentration was  $390.3 \pm 39.7$   $\text{ng}/\text{mL}$ . This data

demonstrated that plasma concentrations achieved with standard doses of cisplatin (equivalent to doses given up to  $75\text{mg}/\text{m}^2$ ) is associated with significant fetal exposure which is consistent with clinical observations such as fetal anemia that has occurred after cisplatin exposure. Correlative studies to evaluate impact on fetal tissue is ongoing.

## ABSTRACT

### LiaR as a Target for Anti-adaptation Antibiotics

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Supported by: Cesar A. Arias, MD, PhD, Department of Infectious Disease; The University of Texas Medical School at Houston – Office of the Dean

Key Words: Antibiotic resistance, enterococci, daptomycin, LiaFSR

**Background:** Antibiotic resistance is a growing public health concern. As bacteria adapt and develop resistance to multiple antibiotics, novel strategies to overcome this phenomenon are urgently needed. Enterococci are multidrug-resistant gram-positive bacteria that often cause serious infections in critically ill and immunocompromised patients. Daptomycin (DAP), a lipopeptide antibiotic, has become a last resort drug against multi-drug resistant *Enterococcus faecium* (Efm), the most recalcitrant of the enterococcal species. However, development of DAP resistance during therapy is a major limitation of the clinical use of this drug. The LiaFSR system is a three-component regulatory system that has been shown to orchestrate the cell envelope response to the attack of antibiotics and antimicrobial peptides in Gram-positive bacteria including enterococci. LiaR is the response regulator of this system and mutations in the gene encoding this protein have been associated with DAP-resistance and tolerance in Efm. Efm HOU503 is a clinical isolate that harbors mutations in LiaRS and is tolerant to DAP action (antibiotic is not capable of killing the organism). We hypothesize that deletion of *liaR* would reverse the DAP tolerant phenotype in Efm503, supporting its major role in antimicrobial resistance in enterococci.

**Methods:** Using the PheS\* counter-selection system, we generated a *liaR* non-polar deletion mutant of Efm HOU3. Flanking regions of *liaR* were amplified and cloned into pHOU1 vector using *E. coli* 1000 as the host. The recombinant plasmids were electroporated into *E. faecalis* CK111 and introduced into *E. faecium* 503 (made fusidic acid [FA] resistant) by conjugation. First integrants were selected in the presence of gentamicin 200µg/ml and second recombination events were evaluated in the presence of p-Chl-phenyl-alanine. Candidate colonies were screened by PCR and the deletion was confirmed by sequencing. Pulsed field gel electrophoresis (PFGE) was performed in order to confirm that the mutant was a derivative of Efm HOU503. Additionally, the mutant strain was characterized by determining DAP MICs (using Etest on Mueller-Hinton agar supplemented with Calcium) and growth kinetics.

**Results:** Deletion of *liaR* produced a 30 fold decrease in the minimum inhibitory concentration of DAP for strain Efm HOU503 (3 to .094). The *liaR* mutant did not display a growth defect compared to its parental strain (Efm HOU503 FA) and the PFGE pattern was indistinguishable from Efm HOU503 FA and Efm HOU503, confirming the genetic relatedness of the strains.

**Conclusions:** Our results provide further evidence that LiaR is an important mediator of antimicrobial resistance in Efm emerging as a novel target to develop anti-adaptation antibiotics with the goal of restoring susceptibility to currently used antimicrobials.

## ABSTRACT

### Plasma Resuscitation Protects Endothelial Cells from Apoptosis

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Supported by: Tien C. Ko, MD, Department of Surgery

Key Words: FFP, Apoptosis, Human pulmonary microvascular endothelial cells, LR, HS

**Introduction:** Hemorrhagic shock (HS) is the leading cause of preventable death in trauma worldwide, accountable for 40% of civilian and 66-80% of military deaths. Resuscitation with fresh frozen plasma (FFP) is associated with improved patient survival compared to conventional Lactated Ringer's (LR) solution. However the underlying mechanisms remain unclear. HS is associated with endothelial cell (EC) dysfunction, including increased permeability and apoptosis. Previous studies from our group demonstrate that FFP inhibits tumor necrosis factor (TNF)- $\alpha$ -induced EC permeability, thus contributing to endothelial integrity. We hypothesize that FFP also contributes to endothelial integrity by protecting ECs against apoptosis induction.

**Experimental Design and Methods:** Apoptosis induction in human pulmonary microvascular endothelial cells (HPMECs) was first optimized using an apoptosis-inducer Staurosporin (STS) at different time points and doses. HPMECs were then divided into four treatment groups: 1) vehicle; 2) FFP only; 3) STS only; and 4) STS+FFP. The STS+FFP groups were further divided and treated with different doses of FFP for 30 minutes after STS treatment. Apoptosis was assessed by detection of caspase 3/7 activity.

**Results:** STS induced a time- and dose-dependent apoptosis compared to vehicle control, with the peak induction of apoptosis at 3 hours' treatment with 1 $\mu$ M of STS, which was applied to the following experiments. FFP treatment decreased STS-induced EC apoptosis in a dose-dependent fashion compared to vehicle control, with 1, 0.76, 0.35, 0.18, and 0.09-fold apoptosis induction respectively to 0, 5, 10, 30, and 50% FFP ( $p < 0.05$ ).

**Conclusions:** Our data demonstrate that FFP protects ECs from apoptosis induction, which may contribute to the beneficial effects of FFP resuscitation in hemorrhagic shock by preserving endothelial integrity. Future experimentation is required for the underlying molecular mechanistic studies that may lead to identification of key components responsible for the beneficial effects of FFP and improvement of resuscitation regimen for HS patients.

## ABSTRACT

### SIK1, a Potential Target for Type 2 Diabetes Therapy

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases,  
2T35DK007676-21A1

Key Words: Thermogenesis, Diabetes, SIK1

Brown adipose tissue performs lipolysis, thermogenesis, and utilizes large amounts of glucose. Increased BAT activity could ameliorate type 2 diabetes by increasing energy expenditure. *Ucp-1* is a thermogenic gene expressed in BAT, and increased UCP-1 activity has been effective in reducing adiposity and improving insulin sensitivity in mice, likely because UCP-1 increases energy expenditure by dissipating the proton gradient generated during oxidative phosphorylation. The transcription factor CREB stimulates expression of *Ucp-1*, and salt inducible kinases (SIK1-3) are known to inhibit CREB-dependent transcription. The Berdeaux Lab has found that SIK1 global knockout mice exhibit desirable metabolic characteristics such as increased thermogenesis, decreased brown adipose tissue lipid content, and increased thermogenic gene expression (Nixon, et al, in preparation). However, the specific tissue in which SIK1 exerts its effect has yet to be identified. We hypothesized that SIK1 cell-autonomously inhibits thermogenesis in brown adipocytes, and that alleviating this inhibition by *Sik1* gene deletion specifically in fat would result in increased thermogenesis. We found that adipose-specific *Sik1* knockout mice do not mimic the increased core body temperatures or *Ucp-1* expression exhibited by global knockout mice. Thus, SIK1 does not exert its anti-thermogenic effect by acting directly in brown adipocytes and must act through another tissue. Although the adipose-specific *Sik1* knockout mice do not display increased thermogenesis, they gain weight similarly to control mice when fed a 60% high fat diet for 10 weeks. This finding indicates the loss of *Sik1* in the adipose has neither protected nor predisposed the animals to weight gain after eating a high fat diet. These data suggest that SIK1 action must be inhibited in another tissue in order to observe metabolic improvements.

## ABSTRACT

### Donor Plasma Effects on Platelet Function

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Sponsored by: Charles Wade, PhD, Department of Surgery

Supported by: Charles Wade, PhD, Department of Surgery; The University of Texas Medical School at Houston—Office of the Dean

Key Words: Fresh frozen plasma, platelets, coagulation

**Introduction:** We and others have demonstrated a significant decrease in platelet count and function within 2 to 3 hours following admission in severely injured trauma patients after transfusion. The decrease in platelet function is in part due to the reduction in platelet count. However, the decrease in function does not always equal the decrease in count observed in trauma patients. We investigated whether transfusion of plasma was another factor contributing to platelet hypofunction following trauma.

**Methods:** Whole blood samples were taken from healthy volunteers and their baseline platelet function assessed by impedance aggregometry in response to ADP, collagen, thrombin receptor-activating peptide (TRAP), arachidonic acid (AA) and ristocetin using Multiplate Analyzer. Blood samples were then diluted by 30% using the volunteer's autologous plasma, autologous plasma that was snap frozen and thawed (autologous FFP), and donor FFP from Gulf Coast Regional Blood Center. The percent change in platelet function compared to whole blood or autologous FFP was calculated. FFP from five different donors were used to obtain the average change in function. A student's *t* test with significance set at  $p < 0.05$  was used to determine if dilution, freezing and the use of donor FFP had an effect on platelet function.

**Results:** Dilution of whole blood with autologous plasma by 30% showed a significant decrease of 30% in platelet function in response to all agonists, as expected, with the exception of TRAP. Autologous FFP had no additional effect on platelet function, with the exception of a reduction in TRAP ( $p=0.007$ ). Single donor plasma demonstrated a further reduction in ADP ( $p=0.02$ ), collagen ( $p=0.006$ ) and AA ( $p=0.007$ ) compared to autologous FFP. Finally, comparison across multiple donors ( $n=5$ ) demonstrated a trending, although not significant, reduction in platelet function in response to all agonists with the exception of ristocetin, which remained unchanged.

**Conclusion:** Dilution is the major contributor in the decrease in platelet function however, donor plasma may have additional negative effects on platelet function following transfusion.

## ABSTRACT

### Pilot Study for the Feasibility of Ultrasound in Airway Anatomy Assessment

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Key Words: Airway, Ultrasound, SGA

**Background:** Ultrasound is a key diagnostic tool that can be used to evaluate the airway.<sup>1</sup> Bony and cartilaginous landmarks (hyoid bone and epiglottis, thyroid, and cricoid cartilages) are easily visualized with ultrasound in live and cadaveric models.<sup>2,3</sup> Additionally, sonographic assessment of hyomental distance is predictive of a difficult airway for endotracheal intubation.<sup>4</sup> Other imaging modalities have been successfully used to assess the airway: MRI can successfully visualize placement of supraglottic airway devices.<sup>5</sup> Other imaging studies show good agreement between airways measurements using Computed Tomography and ultrasound.<sup>6</sup>

However, there are conflicting results on the quality, accuracy, and value of ultrasound. Previously, colleagues have compared external measurements to sonographic measurements with mixed results.<sup>7,8</sup> Also, prior investigation found differences in measurements of external landmarks taken with a measuring tape and a digital caliper, as tape measures conform to the neck and digital calipers are more rigid.<sup>9, 10</sup> With these limitations of current methods, ultrasound may be a more accurate and practical way landmarks can be measured based on their exact anatomical location, without neck contours and soft tissue structures of the neck obstructing measurements.

**Methods:** A total of 5 healthy adult volunteers (3 female, 2 male) were recruited. The volunteers extended their neck in a “sniffing position. External airway landmarks were gently palpated and measured (in cm) with a disposable tape measure. Then, ultrasound assessment using a 12MHz linear transducer (Sonosite M-Turbo) attempted to visualize the same landmarks as before using sagittal views for all but transverse views for thyroid width and additional transverse measure of the vocal folds. Measurements were then taken with ultrasound machine program’s caliper (in cm) for all identifiable anatomical once the image had been captured on the system.

**Results:** 5 of the 8 anatomical landmarks were successfully visualized on ultrasound on all volunteers (hyoidmental, hyoid thyroid, thyroid height, thyroid cricoid, and thyroid width). Thyromental distance was successfully visualized on 1 of 5 volunteers. Hyoid cricoid distance



was successfully approximated using anatomical summations on 2 of 5 volunteers. There is significant variation in the measurements in done by tape measure compared to ultrasound. Sonographic measurement of the vocal folds was successful on 4 of the 5 models. Sternomental distance could not be reasonably measured via ultrasound.

**Discussion:** The ease of measuring the vocal folds and with ultrasound provides a new measurement that provides direct measurement of the laryngeal inlet where an SGA sits and could be used in the future to visualize SGAs places in vivo during surgery. The width of the 12 MHz transducer (4 cm) is a limitation to capturing certain anatomical features such as hyoid cricoid distance and thyromental distance; however, composite measurements could be a used to sum 2 measurements (summing hyoid to thyroid notch and thyroid cricoid distance for Hyoid Cricoid distance). The variation between the ultrasound measurements and tape measurements needs to be further explored as soft tissue structures can disrupt tape measurements. For example, thyroid width of ultrasound is measured internally and directly from lateral borders of the thyroid cartilage as opposed to across the neck with the tape measure. The results are promising for prediction of internal airway size and airway device sizing, but further investigation and refinement of ultrasound protocol is warranted.

## **ABSTRACT**

### **Truncated STIM1 Protein Affects Lymphocyte Calcium Signaling in Stroke Prone Hypertensive Rats**

CONNOR GRIFFIN

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*Class of 2017*

Sponsored by: Peter Doris, Ph.D., IMM-Center For Human Genetics

Supported by: National Institute of Diabetes and Digestive and Kidney Disease,  
2T35DK007676-21A1

Key Words: Hypertension, Stroke, Lymphocytes, STIM1, Calcium

Although hypertension often results in heart failure, stroke, and kidney failure, many hypertensive patients are spared these complications for reasons that are not understood. To study this phenomenon, we compared two closely related spontaneously hypertensive rat lines, SHR-A3 and SHR-B2, that greatly differ in their susceptibility to stroke and kidney disease. SHR-A3 rats exhibit high mortality from early onset stroke and kidney failure, whereas SHR-B2 rats are relatively spared from these complications. Genetic mapping indicates that 17% of this phenotypic difference is attributable to genetic variation on chromosome 1, in a region harboring the stromal interaction molecule 1 (STIM1) gene. This variation includes a stop-gained mutation resulting in expression of a truncated STIM1 in SHR-A3 rats. STIM1 activates store-operated  $\text{Ca}^{2+}$  entry (SOCE), which is important for lymphocyte signaling and immune system function. This is demonstrated by humans with loss-of-function mutations of STIM1 who develop severe immunodeficiency and concurrent autoimmune disease. SHR-A3 rats exhibit immune cell infiltration in their damaged kidneys, but are not overtly immunodeficient. Therefore, we hypothesized that the truncated STIM1 protein confers impaired but not absent SOCE in SHR-A3 lymphocytes compared to the full-length STIM1 protein in SHR-B2 rats. Lymphocytes were harvested from both rat lines, and analyzed with Fura-2 single-cell fluorescence intracellular  $\text{Ca}^{2+}$  imaging. Cellular  $\text{Ca}^{2+}$  stores were depleted by incubation in  $\text{Ca}^{2+}$ -free media and treatment with thapsigargin ( $2\mu\text{M}$ ). SOCE was measured in at least 40 lymphocytes from three rats of each rat line as the difference in base to peak intracellular  $\text{Ca}^{2+}$  level following reintroduction of  $\text{Ca}^{2+}$  in the media. SHR-A3 rats exhibited a mean peak SOCE that was 41.7% of that seen in SHR-B2 rats, but still present ( $p < 0.05$ ). This result indicates that the truncated STIM1 in SHR-A3 is functional, but elicits impaired SOCE in lymphocytes compared to the full-length STIM1 in SHR-B2 rats. The reduced SOCE in SHR-A3 could alter immune function in SHR-A3 and promote autoimmune-mediated renal injury process in SHR-A3 rats. Further studies to link the impaired  $\text{Ca}^{2+}$  signaling to altered cytokine expression in activated lymphocytes would confirm that this mutation contributes to altered immune function in SHR-A3.

# ABSTRACT

## The Natural History of Leigh Syndrome

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Sponsored by: Mary Kay Koenig, MD, Department of Pediatrics

Supported by: Mary Kay Koenig, MD, Department of Pediatrics

Key Words: Leigh syndrome, mitochondrial disease, natural history

Leigh syndrome is a hereditary neuro-metabolic disease resulting from mitochondrial dysfunction. Diagnosis relies on the triad of bilateral, symmetric, midline MRI lesions in a patient with neurologic symptoms and lactic acidosis. Patients typically present before the age of 2 years. Despite being one of the more common mitochondrial disorders, once a patient is diagnosed with Leigh syndrome, little is known about the disease course that they will face. The symptoms that develop can range from ophthalmoplegia to respiratory failure; and while some patients maintain a relatively stable baseline, others experience episodic regressions. Utilizing the UT mitochondrial database we undertook the task of describing the natural history of this devastating condition.

By analyzing data gathered from patient medical records, as well as from patient phone conversations, we characterized the distribution of symptoms, MRI findings, and disease progression among the 34 patients seen at the Leigh clinic at the UT Mitochondrial Center of Excellence. The median age of onset was 11.5 months, with more than 60% of patients initially presenting with motor symptoms. Despite the fact that Leigh syndrome is genetic, a specific mutation was identified in only 62% of our patients, with 41% having mitochondrial mutations and 21% having nuclear mutations.

We found that regressions in health or skills are present in nearly 80% of patients, with approximately half of these patients having episodic regressions and the other half having a more steadily progressive disease course. On MRI images, 68% of patients had lesions in the basal ganglia. Over the entire course of their disease, 76% were hypotonic, 68% had feeding problems with 78% of these patients eventually requiring a feeding tube, and 56% had respiratory symptoms.

We conclude that although Leigh syndrome can be heterogeneous in its presentation, there are common elements that occur in all patients. This snapshot of the Leigh syndrome patient population at the UT Leigh syndrome clinic lays the foundation for creating a national database for Leigh syndrome patients to further outline the natural history of this disease.

## ABSTRACT

### Heart Rate Variability in Pediatric Traumatic Injuries

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*Class of 2017*

Sponsored by: Linda Ewing-Cobbs, PhD, Pediatrics & Psychiatry and Behavioral Sciences  
Children's Learning Institute

Supported by: RO1 NS43608 from the National Institutes of Health; The University of Texas  
Medical School at Houston- Office of the Dean

Key Words: TBI, heart rate variability, stress, parasympathetic, sympathetic

People with traumatic brain injuries (TBI) and orthopedic injuries have shown higher rates of post-traumatic stress symptoms (PTSS). The excess vigilance and hyper arousal seen in those with PTSS are believed to be caused by over exertion of the sympathetic nervous system compared to that of the parasympathetic nervous system. Measurement of heart rate variability (HRV), which is the oscillation of times between the RR peaks in an ECG, can be used as an index of the sympathovagal balance. While TBI and extracranial injuries are common, little is known about how these traumatic pediatric injuries alter autonomic function or how change in autonomic function influences the development of PTSS. We posited that both injury groups, TBI and extracranial injuries, would demonstrate a lowered HRV compared to that of the healthy comparison group and that lower HRV will be associated with increased stress symptoms. Participants were drawn from a longitudinal, prospective study of subjects in three groups: 1) mild to severe TBI (n=34), 2) extracranial traumatic injuries (n=21), and 3) a healthy comparison group (n=29). Both injured groups consisted of children ages 8-15 injured during a motor vehicle collision and admitted to the Pediatric Trauma Service at the Level 1 Pediatric Trauma Center at Children's Memorial Hermann Hospital. Six months after the injury, HRV Live! Continuous Heart Rate Variability Monitoring System was placed on the earlobe of the participant to monitor the HRV of each child in the sitting position at five-minute intervals before, immediately after, and 30 minutes after the completion of the Trier Social Stress Test. Due to poor recording quality, six of the participants were removed from data analysis. During this testing period, the child was given a Child Post Traumatic Stress Disorder Symptom Scale questionnaire of twenty questions to assess for traumatic stress markers: re-experiencing, avoidance, and autonomic arousal. SDNN, the standard deviation of normalized R to R peaks from an ECG, was used as a measure of the variability; an increase in SDNN indicates an increase in HRV. SDNN did not vary significantly across groups,  $F(2, 77) = 0.35, p > .1$ . Scores changed over time,  $F(2, 77) = 4.99, p = .009$ . For the extracranial injury group, Spearman correlation coefficients indicated that the difference scores of SDNN before and after the TSST-C were significantly correlated with avoidance,  $r_s = -.616, p = .006$ , arousal,  $r_s = -.692, p = .001$ , and re-experiencing scores,  $r_s = -.648, p = .004$ . For the TBI group, there was no significant relation of SDNN with any stress scores. HRV increased over time in all groups following the TSST-C, implying parasympathetic input calmed the child after the stressful event. In the extracranial injury group, children with more PTSS had the least change in HRV during exposure to the stressor. The correlation amongst the extracranial injured group may indicate that injury-related PTSS are due to greater autonomic response.

## ABSTRACT

### The Emergency Department: A Unique Environment for Potential Obesity Prevention

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Sponsored by: Mona Eissa, MD, PhD, MPH, Department of Pediatrics

Supported by: The University of Texas Medical School at Houston- Office of the Dean

Key Words: Pediatrics, Obesity, Emergency Medicine

**Context** Childhood obesity is a high priority for public health and government officials because of its steady rise in prevalence. Various studies have researched the immediate and long-term consequences of childhood and adolescent obesity, giving weight to its large clinical significance. Despite the abundance of knowledge available regarding pediatric obesity, little research has been conducted on pediatric obesity in the realm of emergency medicine.

**Objective** To determine the prevalence of normal, overweight, and obese pediatric patients amongst the patient population of Memorial Hermann's ED. To assess for a relationship between the following variables and obesity by comparing obese and non-obese patients: ethnicity; gender; insurance status; admission rates; discharge diagnosis; time spent in the ED.

**Design, Setting, and Patients** Retrospective, observational study of medical records of children, ages 2 to 18, entering the Emergency Department at Memorial Hermann beginning on June 1<sup>st</sup>, 2014 to July 15<sup>th</sup>, 2014. Inclusion criteria included children 2 to 18 years of age with well-documented height and weight measurements. BMI and BMI percentile were calculated for each child included in the study using formulas recommended by the Center for Disease Control, which defines obesity as equal to or greater than the 95<sup>th</sup> percentile; overweight as between the 94<sup>th</sup> or 85<sup>h</sup> percentile; and normal weight as between the 84<sup>th</sup> to 5<sup>th</sup> percentile. Summary statistics as well as Chi-squared and Fisher tests, were used to determine association between the patient's determined weight class (normal, overweight, obese) and other variables.

**Results** Of the 503 patients meeting inclusion criteria, 63% were of normal weight (317), 15% were overweight (76), and 22% were obese (110). Of the 251 males, 23% were considered obese, as compared to 21% of the 252 females. Of those falling into the obese category, 29% were African American, 46% were Hispanic, and 20% were Caucasian. Similar numbers were seen with overweight pediatric patients: 29% African American, 42% Hispanic, and 26% Caucasian. No statistical evidence was found to support an association between BMI percent, discharge diagnosis, insurance status, or admission status.

**Conclusions** This particular study exhibited a large proportion of obese children compared to the national average of 17%, as calculated by the CDC, with a large proportion belonging to minority groups. Because childhood obesity is such an important indicator of future health, further research must be conducted on how to intervene and implement weight reduction strategies, especially within minority groups. The high rates of overweight and obese children visiting the Emergency Department lend a unique opportunity for Emergency Medicine physicians to implement preventive care early.

## ABSTRACT

### Evaluation of Factors Associated with Lack of Retention in Care in HIV Patients

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Sponsored by: Rodrigo Hasbun, MD, MPH, Department of Infectious Disease

Supported by: Rodrigo Hasbun, MD, MPH, Department of Infectious Disease

Key Words: Retention in care, HIV, Montreal Cognitive Assessment

**BACKGROUND:** Lack of retention in care of patients with human immunodeficiency virus (HIV) is associated with many adverse patient outcomes such as antiretroviral therapy failure and death. Little is currently known about the factors that might contribute to the lack of retention in care in HIV patients. Therefore we investigated using a retrospective study looking at 138 patients at Thomas Street Clinic to see if patients were retaining care and which factors were associated with lack in retention in care in these patients.

**METHODS:** In this retrospective, observational study we studied 138 patients enrolled at Thomas Street Clinic. The first step in the analysis was to define if patients were retaining care. In this study we defined retaining care by utilizing the Health Resources and Services Administration HIV/AIDS Bureau (HRSA HAB) definition for care retention. Retaining care is defined as a patient that has 2 kept visits separated by more than 90 days during the follow up 12-month period. The next step was screening all 138 patients for co-existing conditions such as; syphilis, active drug use, hepatitis B and C, *Toxoplasma gondii*, tuberculosis exposure, and depression. All patients also underwent a complete battery of neuropsychological tests including the Montreal Cognitive Assessment (MOCA), Symbol digit modalities test, Stroop Color and Word test, and Beck Depression Inventory-II to evaluate various cognitive domains. Statistical analysis was conducted comparing all of the possible co-existing conditions and neuropsychological test scores to see if any were associated with lack in retention in care. Statistical analysis was conducted using SPSS version 19 (SPSS). Bivariate analysis was conducted by using the Pearson's X<sup>2</sup> test or Fisher's exact test to identify factors that were significantly associated with neurocognitive impairment ( $P < 0.05$ ).

**RESULTS:** A total of 138 patients were enrolled in the study. The data showed 76 (55.1%) patients met the criteria of retaining care, while 62 (44.9%) patients were not retaining care. Variables that were found to predict retention in care were patients being over the age of 50 (19/26= 73.1% for patients that retained care and 7/26=26.9% for patients that did not retain care,  $p=0.04$ ). A MOCA score less than 26 also predicted retention in care (63/100=63% for patients that retained care and 37/100=37% for patients that did not retain care,  $p=0.002$ ). Patients that had a co-infection of Hepatitis B were found to be less likely to retain care (16/39=41% for patients that retained care and 23/39=59% for patients that did not retain care,  $p =0.047$ ).

**CONCLUSIONS:** Lack of retention in care proved to be a pervasive problem at Thomas Street Clinic that affected almost half of all patients. Identifying patients who are not retaining care is of major importance because of the adverse outcomes associated with lack of care retention. Further investigation should be done to better predict factors that may put patients at risk for not retaining care.

## ABSTRACT

### Obesity and Airway Responses to Ozone: The Role of Chemerin

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Sponsored by: Richard A. Johnston, Ph.D., Department of Pediatrics

Supported by: National Institute of Diabetes and Digestive and Kidney Disease,  
2T35DK007676-21A1

Key Words: asthma, chemerin, obesity, and airway hyperresponsiveness

**Rationale.** Obesity and air pollution are major public health problems in the developed and developing world. Obesity enhances airway responsiveness to methacholine following exposure to ozone (O<sub>3</sub>), a common air pollutant and an asthma trigger. However, the mechanistic basis underlying this phenomenon has yet to be elucidated. Chemerin, a pro-inflammatory hormone and cytokine, is secreted by adipocytes, increased in the serum of obese subjects, and elevated in the lung following O<sub>3</sub> exposure. Since chemerin is pro-inflammatory, and O<sub>3</sub>-induced airway hyperresponsiveness (AHR) is mechanistically to several aspects of O<sub>3</sub>-induced airway inflammation, we hypothesized that chemerin contributes to the development of O<sub>3</sub>-induced AHR. To test our hypothesis, we measured airway responsiveness to methacholine in mice genetically deficient in chemerin (chemerin-deficient mice) and lean, wild-type (C57BL/6) mice. **Methods.** Male and female chemerin-deficient mice and age- and gender-matched, wild-type C57BL/6 control mice were exposed to either filtered room air (air) or O<sub>3</sub> [2 parts/million] for three hours. Twenty-four hours following the cessation of exposure, the mice were anesthetized and instrumented for the measurement of airway responsiveness to methacholine using the forced oscillation technique. To assess airway responsiveness, we used indices of airway [airway resistance (R<sub>aw</sub>)] and lung parenchymal [the coefficient of lung tissue damping (G) and the coefficient of lung tissue elastance (H)] oscillation mechanics. **Results.** Following exposure to air, responses to methacholine for R<sub>aw</sub>, G, and H were significantly greater in chemerin-deficient as compared to wild-type mice at the highest dose of methacholine (100 mg/ml). However, no genotype related differences in response to methacholine for R<sub>aw</sub>, G, and H occurred at any other dose of methacholine. O<sub>3</sub> exposure significantly increased responses to methacholine for R<sub>aw</sub>, G, and H in both chemerin-deficient and wild-type mice when compared to genotype-matched, air exposed controls. However, following exposure to O<sub>3</sub>, responses to G were significantly greater in chemerin-deficient as compared to wild-type mice. **Conclusion.** Contrary to our hypothesis, these results demonstrate that chemerin ameliorates O<sub>3</sub>-induced AHR, and thus, obesity-induced elevations in chemerin may serve a protective role in dampening lung dysfunction that is exacerbated by obesity. Furthermore, these results suggest that chemerin or chemerin analogues may serve as useful therapeutics to ameliorate O<sub>3</sub>-induced AHR in both normal weight and obese individuals.



## **ABSTRACT**

### **MicroRNA-601 and -632 Inhibit Proprotein Convertase Subtilisin/Kexin Type 9 Expression in Human Hepatocytes and Glioblastoma Cells**

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Sponsored by: Ba-Bie Teng, PhD, Center for Human Genetics, The Brown Foundation Institute of Molecular Medicine (IMM)

Supported by: National Institute of Diabetes and Digestive and Kidney Disease, 2T35DK007676-21A1

Key Words: PCSK9, miRNA, atherosclerosis

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a hyperlipidemia drug target, regulates circulating low-density lipoproteins (LDL) by binding to hepatocyte LDL receptors (LDLR) and by inhibiting apolipoprotein B degradation. In addition to promoting hepatic atherosclerotic factors, PCSK9 has critical functions in other tissues such as regulating neuronal apoptosis and lipid metabolism. To develop improved PCSK9 targeting therapies against hyperlipidemia and atherosclerosis, a better understanding of PCSK9 function in all tissues and methods to manipulate its expression are necessary. Therefore, endogenously expressed microRNAs (miRNAs) directly targeting PCSK9 were studied. To delineate PCSK9 regulatory miRNA(s), candidates complementary to the PCSK9 3' untranslated region (3'-UTR) were first identified. Initial screening of these candidates was performed with a firefly luciferase assay on COS1 cells transfected with miRNA candidates and vectors containing the PCSK9 3'-UTR downstream from a firefly luciferase reporter gene. Regulation by screened candidates in HepG2 and U87 cells was then studied after confirmation of PCSK9 expression in each cell line. Following 48 hours transfection with candidate miRNAs, changes in PCSK9 mRNA and cell lysate protein expression were determined through qPCR and western blotting. MiRNA-601 and -632 were shown to interact with the PCSK9 3'-UTR in the luciferase assay. A decrease in PCSK9 mRNA expression was observed only with miRNA-601 transfection in HepG2 cells and with both miRNAs in U87 cells. A decrease in PCSK9 protein expression in cell lysates was observed following both miRNA-601 and -632 transfection in both HepG2 and U87 cells. These results indicate that miRNA-601 and -632 may play a significant role of regulating PCSK9 in tissues such as liver and brain. Manipulation of these miRNAs may lead to better understanding of PCSK9 in lipid metabolism and its role in the brain. A better method of safely reducing risks of hyperlipidemia and atherosclerosis is warranted.

## ABSTRACT

### MicroRNA-601 and -632 Inhibit Proprotein Convertase Subtilisin/Kexin Type 9 Expression in Human Hepatocytes and Glioblastoma Cells

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Sponsored by: Michelle K. McNutt, MD, FACS, Department of Surgery, John B. Holcomb, MD, FACS, Department of Surgery and Director of the Center for Translational Injury Research

Supported by: Center for Translational Injury Research (CeTIR); The University of Texas Medical School at Houston- Office of the Dean

Key Words: Blunt cerebrovascular injury (BCVI), ischemic stroke, antithrombotic therapy

**BACKGROUND:** Blunt cerebrovascular injury (BCVI) is defined as injury to the vertebral or carotid artery as a result of blunt trauma and is diagnosed in approximately 1% of blunt trauma patients. Although BCVIs comprise only a fraction of the trauma population, these injuries predispose patients to devastating neurologic sequelae, specifically ischemic strokes. Studies within the last decade have shown that rapid diagnosis and early antithrombotic treatment can greatly reduce the incidence of BCVI-related stroke to 0.5%. However, these management guidelines have only been delineated for isolated cases of BCVI. Given the common mechanisms of blunt injury, such as motor vehicle collisions, the majority of BCVIs present with concomitant injuries - traumatic brain injury, solid organ injury, and spinal cord injury - that may delay the initiation of antithrombotic therapy. The purpose of this study was to evaluate the incidence of stroke in isolated cases of BCVI in comparison to cases of BCVI complicated by concomitant injuries, determine the incidence of bleeding complications as a result of antithrombotic therapy, and assess the timing of BCVI treatment initiation.

**METHODS:** Electronic medical records and the trauma registry from Memorial Hermann Hospital (MHH) were utilized to identify a cohort of blunt trauma patients diagnosed with BCVI for this retrospective study. Inclusion criteria included an age greater than 16 and a BCVI diagnosis via a multi-slice CTA of the neck at MHH between August 2009 and January 2014. The incidence of stroke, determined via review of CT and MRI brain findings, was calculated for both isolated and complicated BCVI patient groups. Fisher's exact and Wilcoxon statistical analyses were used to further compare isolated and complicated BCVI groups for time to diagnosis and time to treatment, and p-values of <0.05 were accepted as significant.

**RESULTS:** A total of 323 patients were included in the analyses of this study demonstrating a BCVI incidence of 1.1% among the MHH blunt trauma population. Within the study cohort 34.4% (111/323) were isolated cases of BCVI and 65.6% (212/323) were complicated cases of BCVI. The isolated and complicated BCVI patient groups had identical stroke rates of 9.9% (11/111; 21/212). The complicated BCVI cohort was found to have a significantly shorter median time from injury to diagnosis of BCVI (1.9 hrs,  $p < 0.001$ ), and a significantly longer median time from diagnosis of BCVI to initiation of treatment (55 hrs,  $p < 0.001$ ). Moreover, the

rate of bleeding complications following the initiation of BCVI treatment was 0.3% (1/323).

**CONCLUSION:** Despite a delay in the initiation of antithrombotic therapy in complicated BCVI patients, stroke rates remained identical for the isolated and complicated BCVI groups. The low incidence of bleeding complications due to BCVI treatment suggests that these delays in the initiation of treatment may not be warranted. However, future studies such as a multicenter prospective trial are still needed to elucidate optimal management strategies for cases of BCVI complicated by concomitant injuries.

## ABSTRACT

### Gene Implicated in ALS Causes Depletion of Endoplasmic Reticulum Ca<sup>2+</sup> Stores

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Supported by: Kartik Venkatachalam, PhD, Department of Integrative Biology and Pharmacology; The University of Texas Medical School at Houston- Office of the Dean

Key Words: Amyotrophic lateral sclerosis, Endoplasmic Reticulum (ER), Ca<sup>2+</sup> dysregulation, VAPB

Amyotrophic lateral sclerosis (ALS) is an adult-onset motor neuron disease characterized by progressive loss of motor function (Renton *et al.*, *Nature Neurosci*, 2014). The main cause of death in ALS is respiratory failure that typically occurs 2-3 years after the onset of symptoms. Currently, the biochemical alterations underlying ALS are incompletely understood and the best pharmaceutical treatment for ALS, riluzole, only lengthens lifespan by 3 months (Renton *et al.*, *Nature Neurosci*, 2014). We propose that the possible mechanisms underlying motor neuron dysfunction in ALS can be explored by studying genes that are known to cause ALS, such as VAPB, which encodes an ER associated protein involved in lipid transport and is responsible for a familial form of ALS (ALS8) when mutated. The mutant form of VAPB (VAPB<sup>P58S</sup>) is thought to compromise the transport of ceramide out of the ER, leading to the accumulation of ceramide in the ER and overactivation of ER calcium channels called ryanodine receptors (RyRs). Overactive RyRs could result in the dysregulation of Ca<sup>2+</sup> homeostasis that may underlie ALS pathology. We hypothesized that, due to overactivated RyRs, ER Ca<sup>2+</sup> stores would be depleted in cells expressing VAPB<sup>P58S</sup>. To test this hypothesis, both wild type VAPB<sup>WT</sup> and VAPB<sup>P58S</sup> were cloned into a vector (PcDNA3.1) that was then transfected into a mouse neuronal cell line (Neuro-2a). These transfected cells were loaded with the Ca<sup>2+</sup> indicator, Fura-2, that is used to measure the cytosolic Ca<sup>2+</sup> concentration. The cells were then treated with a SERCA pump inhibitor (thapsigargin) that effectively releases ER Ca<sup>2+</sup> stores. The results showed that cells transfected with VAPB<sup>P58S</sup> released a smaller amount of Ca<sup>2+</sup> from the ER into the cytosol when subjected to thapsigargin compared to WT. The data was subjected to statistical analysis (two-tailed T-test) and was found to be significant (p = 0.016, VAPB<sup>WT</sup> n = 10, VAPB<sup>P58S</sup> n = 8). These results confirmed our hypothesis that ER Ca<sup>2+</sup> stores are depleted in cells expressing a mutated form of VAPB that is responsible for a familial form of ALS.

## ABSTRACT

### The Time Course of p90 Ribosomal S6 Activation in *Aplysia* After Treatment with Serotonin

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Sponsored by: John H. Byrne, Ph.D., Department of Neurobiology and Anatomy

Supported by: National Institute of Neurological Disorders and Stroke, T35 NS 064931-05

Key Words: P90 ribosomal s6 kinase, *Aplysia*, learning and memory

The pathways and processes underlying the formation of long-term memory (LTM) have been extensively studied in the marine mollusk *Aplysia californica*. One main pathway involves the serotonin-induced and cyclic AMP (cAMP)/Protein Kinase A (PKA)-dependent activation of the transcription factor cAMP response element-binding protein 1 (CREB1). CREB1 is a transcription factor that, when phosphorylated by PKA, stimulates the transcription of immediate-early genes involved in the formation of LTM. In some systems, CREB1 can also be phosphorylated at the same site as PKA by p90 ribosomal S6 kinase (RSK), but this pathway has not been examined in *Aplysia*. The objective of my project was to examine this possibility using a combination of western blot analysis and immunofluorescence.

As a first step, I examined the specificity of two commercial antibodies to phosphorylated RSK (pRSK), the active form of RSK. I found that one of the antibodies was likely labeling a separate protein with a similar phosphorylation site. The second antibody, however, proved to be specific to pRSK.

Once the antibody was validated, it was used to investigate the temporal pattern of activation of RSK. To determine the activation time course of RSK, *Aplysia* paired pleural-pedal ganglia and cultured sensory neurons (SNs) were used. The level of pRSK in pleural-pedal ganglia was analyzed through western blotting. One ganglion of the pair was bathed in 50 $\mu$ M serotonin, while a second was bathed in a vehicle solution as a control. A small (6.74 %) increase in pRSK levels was seen in the ganglion treated with serotonin, but additional experiments will be necessary to verify the result. Cultured SNs were also treated with either a 50 $\mu$ M serotonin solution or vehicle solution as a control. Using immunofluorescence and confocal microscopy to analyze pRSK levels at time points of 5, 15, 45 and 60 minutes after treatment, no significant differences between pRSK levels were observed although the sample size was limited. Additional experiments will be needed to determine if there is a point in time at which the level of pRSK is significantly increased from baseline and the extent to which an increase in pRSK affects CREB1.

## **ABSTRACT**

### **Pyruvate Kinase M2: the Driving Force behind Altered Substrate Metabolism in Sunitinib Treated Heart**

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Sponsored by: Heinrich Taegtmeier, MD, DPhil, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Disease,  
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Key Words: Sunitinib-induced cardiotoxicity, PKM2, Warburg effect

#### **Background**

Sunitinib malate (Sutent, Pfizer), a receptor tyrosine kinase inhibitor used to treat highly vascularized solid tumor, causes hypertension and cardiac failure in nearly 50% and 20% of the patients, respectively. Sunitinib also promotes normalization of blood glucose levels in diabetic cancer patients. Since intensive blood glucose lowering may contribute to adverse cardiovascular outcomes in diabetic patients, it is plausible that excessive cardiac glucose uptake contributes to sunitinib-induced cardiotoxicity. One mechanism explaining this effect might be the “Warburg Effect,” a phenomenon observed in cancer cells, driven by the re-expression of pyruvate kinase’s fetal form: PKM2. Indeed, our lab’s prior studies involving sunitinib-treated mice showed that sunitinib increased whole-body glucose disposal and resulted in five- and seven-fold increases in glucose uptake in heart and skeletal muscle, respectively. Accordingly, we hypothesized that the hearts of sunitinib-treated mice and heart failure patients have higher PKM2 expression levels to account for the enhanced cardiac glucose uptake.

#### **Materials and Methods**

**Animals:** Male C57BL6 mice were divided randomly into two groups and treated orally with either sunitinib (40mg/kg/day) or vehicle for 21 days. Hearts were then harvested.

**Human Heart Tissue:** Heart tissues from patients who had undergone left ventricular assisting device (LVAD) implantation were collected at the time of implantation and at either explantation, transplantation, or autopsy. As a control, PKM2 levels were assayed in the non-failing left-ventricular tissue from patients who had undergone double heart-lung transplant due to idiopathic pulmonary hypertension and right-sided heart failure.

#### **Methods**

Masson-Trichrome staining was used to assess for fibrosis and glycogen. Western blots and qRT-PCR were used to analyze PKM2 protein and mRNA levels. ELISA was used to determine serum insulin levels.

#### **Results**

**Animals:** The hearts of sunitinib-treated mice showed greater glycogen stores without significant fibrosis by Masson-Trichrome stain. Correspondingly, these mice exhibited a statistically significant increased level of glycolytic genes such as GLUT1, PDK1, PDK4, LDHA, and PKM2 in addition to lowered serum insulin level.

**Human Heart Tissue:** qPCR and Western blots analysis of LVAD samples revealed a statistically significant increased PKM2 expression level prior to LVAD implantation compared to tissue from the non-failing hearts.

**Conclusions**

The upregulation of PKM2 affords cancer cells greater metabolic flexibility to utilize carbons derived from glucose to synthesize nucleotides and lipids to support proliferation. I now propose that re-expression of PKM2 in cardiomyocytes by sunitinib treatment may drive altered substrate metabolism, resulting in increased uptake of glucose and glycolysis by cardiomyocytes.

## **ABSTRACT**

### **Radiologic-Histological Correlations from Hepatocellular Carcinoma Liver Explants of Transplant Patients**

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Sponsored by: Julie H. Rowe, MD, Department of Internal Medicine - Oncology

Supported by: Julie H. Rowe, MD, Department of Internal Medicine - Oncology

Key Words: Hepatocellular Carcinoma, Radiogenomics, Imaging Characteristics

**OBJECTIVE:** Most malignancies require a pathologic diagnosis for confirmation of cancer whereas the diagnosis of hepatocellular carcinoma (HCC) is done radiographically. Current studies have investigated the concept of “radiogenomics,” which combines the use of dynamic-contrast imaging with next-generation sequencing (NGS) of corresponding tumor tissue to provide prognostic information. Through review of retrospective imaging and collection of clinical data of HCC patients who have undergone orthotopic liver transplantation, we can elucidate certain characteristics that are associated poor outcomes. **BACKGROUND:** Hepatocellular carcinoma is currently the fifth most common type of cancer in the world. Risk factors associated with HCC include hepatitis B and C, alcohol, and non-alcoholic steatohepatitis (NASH). Advancements in HCC treatment have been slow due to reliance on radiographic evidence for diagnosis. In radiogenomics, “radiophenotypes” gathered from non-invasive imaging are linked to gene expression signatures to predict disease progression and recurrence. Kuo et al. showed that HCC imaging phenotypes that correlated with tumor gene signatures that were known to correlate with doxorubicin drug response. We hypothesize that by combining retrospectively collected clinical data and radiologic data, imaging phenotypes could provide prognostic information on recurrence or death and thus then be correlated with the genetic profiles obtained from the HCC liver explant through NGS. **METHODS:** We conducted a retrospective analysis of 106 patients who were diagnosed with HCC and subsequently received orthotopic liver transplantation (OLT) at Memorial Hermann Texas Medical Center - University of Texas Health Science Center Houston between January 1, 2004 and December 31, 2013. Clinical, pathological, radiological data, and outcomes including death and recurrence were collected. Radiologic characteristics including size and number of tumor(s), ill-defined or well-circumscribed, multifocality, presence of macrovascular invasion, arteriovenous shunt, portal vein thrombosis, internal arteries and necrosis, tumor margin score, tumor infiltration, abutment, and bulge, evidence of capsule, hypo-dense halo and enhancement were reviewed by two board-certified radiologists. **RESULTS:** There were 106 patients who underwent OLT due to HCC with 78% male. The median age was 57 (range 39-80). The etiology of HCC included hepatitis C (66%), hepatitis B (8%), alcohol (8%), non-alcoholic steatohepatitis (NASH) (6%), and other (10%). Of the 106 patients, eleven patients had HCC recurrence with 8 having extra-hepatic recurrence. Eighty-four patients received loco-regional treatments with 70% receiving trans-arterial ablation (TACE) of the primary tumor(s).



There were 21 deaths with cause of death due to cancer occurred in eleven patients. The mean size of the largest HCC tumor of the deceased arm was 35.75mm (st. dev 13.41) and 35.66mm (st. dev 18.10) in the living arm. Radiologic data were reviewed but no significant radiographic features were associated with death or HCC recurrence. **CONCLUSION:** Our review of HCC post-liver transplants shows that certain radiologic characteristics previously described as to be prognostic in other HCC patients have a limited application in our cohort of HCC patients who have a better prognosis. The clinical spectrum of HCC is variable with <30% of HCC patients are eligible for liver transplantation. The genetic signatures of these patients should be further elucidated with a focus on the patients who have recurred.

## ABSTRACT

### Prevalence and Impact of Admission Hyperfibrinolysis in Severely Injured Pediatric Trauma Patients

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Sponsored by: Bryan Cotton, MD, Department of Surgery/CeTIR

Supported by: Bryan Cotton, MD, Department of Surgery/CeTIR; The University of Texas Medical School at Houston – Office of the Dean

Key Words: Hyperfibrinolysis, pediatric trauma, rTEG, coagulation

**Introduction:** Hyperfibrinolysis (HF) on admission is associated with increased mortality in adult trauma patients. Several studies have demonstrated that 9% of severely injured adults present to the emergency department (ED) with HF. The purpose of the current study was to (1) define HF in pediatric patients and a relevant cut-point for therapeutic intervention (if any), (2) identify the prevalence of HF in severely injured pediatric patients, and (3) determine if HF on admission is as lethal a phenomenon as it is in adults.

**Methods:** Following IRB approval, we identified all pediatric trauma admissions ( $\leq 17$  years old) that met highest-level trauma activation criteria between 01/2010 and 12/2013. Fibrinolysis rates were determined using LY-30 by rapid thrombelastography (rTEG), which represents the percent reduction of the maximal clot amplitude (fibrinolysis) 30 minutes after such amplitude is achieved. HF was defined a priori as initial LY-30 inflection point that translated to a doubling of mortality. Two previous studies in adults demonstrated an inflection point of  $\geq 3\%$ ; where mortality doubled from 9 to 20%. We began by identifying a relevant inflection point to define HF and its prevalence, followed by univariate analysis to compare HF and non-HF patients. Finally, a purposeful logistic regression model was developed to evaluate predictors of mortality in severely injured pediatric patients.

**Results:** 819 patients met study criteria. LY-30 values were plotted against mortality. A distinct inflection point was noted at  $\geq 3\%$ , where mortality doubled from 6 to 14%. Of note, mortality continued to increase as the amount of lysis increased, with a 100% mortality demonstrated at an LY-30  $\geq 30\%$  (compared to 77% in adults). Using LY-30  $\geq 3\%$ , patients were stratified into HF (n=197) and non-HF (n=622), with prevalence on admission of 24%. With the exception of HF patients being younger (median 11 vs. 15 years;  $p < 0.001$ ), there were no differences in demographics, scene vitals or injury severity scores between the groups. On arrival to the ED, HF patients had a lower systolic blood pressure (median 118 vs. 124 mmHg) and lower hemoglobin (median 12.2 vs. 12.7 g/dL); both  $p < 0.001$ ). Controlling for age, arrival vital signs, admission hemoglobin and injury severity (ISS), logistic regression identified admission LY30  $\geq 3\%$  (OR 6.2, 95% CI 2.47-16.27) as an independent predictor of mortality.

**Conclusion:** Similar to adults, admission HF appears to reach a critical threshold at LY30  $\geq 3\%$  in pediatric patients. Admission HF in pediatric patients occurs more frequently than in adults (24 vs. 9%) but is similarly associated with a doubling in mortality (6 to 14%). Admission LY-30  $\geq 3\%$  carries a 6-fold increased likelihood of mortality in severely injured pediatric patients. HF on admission may serve to rapidly identify those injured children and adolescents likely to benefit from hemostatic resuscitation efforts and to guide anti-fibrinolytic therapy.

## ABSTRACT

### Quantitating *In Vitro* Biofilm Attachment and Proliferation on Diverse Biomaterials with qPCR

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Supported by: Department of Microbiology and Molecular Genetics; The University of Texas Medical School at Houston—Office of the Dean

Key Words: Biofilm, diabetes, biomaterials, *Enterococcus faecalis*, *Staphylococcus Aureus*

Biofilm formation on in-dwelling devices constitutes the most common cause of nosocomial infections in the United States and can be attributed as a major cause of chronic infections. Diabetics are particularly susceptible to these infections due to compromised vascularity in their extremities and a weakened immune response. We have adapted an *in vitro* biofilm model developed in our lab to evaluate biofilm growth on different orthopaedic biomaterials that had been previously used for biofilm growth. Previously used and cleaned steel, Grade 2 type II, Grade 2 type III, and Grade 5 type III anodized titanium alloy discs served as growth substrates for *Enterococcus faecalis* and *Staphylococcus aureus* biofilms, in separate trials. These are the two most common etiological agents of orthopaedic biofilm infections. Unused polymethylmethacrylate (PMMA) bone cement discs served as the control substrate. After the initial inoculation on Day 0 with  $10^6$  *E. faecalis* cells in synthetic interstitial fluid (SIF), on the different biomaterial discs in 24-well plates, the plates were statically incubated at 37°C. The medium was refreshed every day with sterile SIF, in order to supply fresh nutrients to the biofilms. On days 1 - 7, the DNA from three discs of each biomaterial was extracted separately and subjected to quantitative PCR (qPCR) to determine the number of cells attached to each disc. Also, on each day one disc of each substrate was stained with live/dead dyes and imaged using a fluorescence microscope. The results of these experiments are compared to previous results from our lab in which confocal microscopy was used to estimate the bacterial attachment to unused surfaces of the same biomaterials by determining biovolume of the live stained cells. The previous results were more varied for *E. faecalis* than for *S. aureus* and found that titanium discs supported the most biofilm growth. Our recent results using the qPCR method indicate that after 1 day of biofilm growth a similar number of the *E. faecalis* cells ( $\sim 1 \times 10^9$ ) were generally attached to the different biomaterials, although steel had a consistently greater number of attached cells ( $5 \times 10^9$ ). The fluorescence microscopy revealed what appeared to be a developmental program in which microcolonies observed during days 2 to 4 grew into relatively uniform lawns of attached cells on the surfaces of the different biomaterials by days 5 to 7. Future analysis of *S. aureus* biofilm formation is planned.

## ABSTRACT

### Evaluation of the Arcuate Fasciculus in Ischemic Stroke Patients Treated with Stem Cell Therapy

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Supported by: The University of Texas Medical School at Houston – Office of Educational Programs

Key Words: Diffusion Tensor Imaging, Autologous Mononuclear Cells, Arcuate Fasciculus

**Background:** Tissue plasminogen activator (tPA) is the most effective therapy for patients with ischemic strokes, if administered within 3.0 to 4.5 hours. However, therapy to promote post-stroke neuronal restoration is limited. Aphasia is an impairment that can occur after a stroke, leading to a reduction in language comprehension and verbal communication. Microstructural damage to the arcuate fasciculus (AF), a part of the superior longitudinal fasciculus white matter tract, is responsible for these deficiencies. Autologous bone marrow derived mononuclear cells (MNCs) transplantation is an experimental treatment for ischemic strokes. Clinical trials for MNCs transplantation have shown that it is a safe and achievable therapy. The next phase for this therapy requires defining and measuring the mechanisms of action. The National Institutes of Health Stroke Scale (NIHSS), a clinical assessment that can be used to assess the severity of aphasia, can be subjective and does not provide visual microstructural and functional information. Diffusion tensor imaging (DTI) uses the diffusion of water molecules as a tracer to provide information about microstructural properties of tissues, which allows for visualization and quantification of structural changes in white matter tracts. DTI derived metrics of the arcuate fasciculus tract will not only aid in understanding recovery after a stroke, but it can also serve as a quantitative neuroimaging marker for novel therapy.

**Objective:** The primary objective of this research was to develop longitudinal neuroimaging biomarkers that can qualitatively and quantitatively assess post-therapeutic progression or regression, and correlate this data with a clinical assessment.

**Method:** Fractional anisotropy (FA) and mean diffusivity (MD) are two DTI matrices used to quantify the integrity of AF tracts and dynamic changes in axonal density, respectively. Twenty-five patients with ischemic strokes (IS) were enrolled in this experimental therapy; however, only eleven patients who completed the follow-up imaging at 1, 3, 6, 12, and 24 months were further evaluated in this study. The serial infarct volume was measured by manual delineation. Bone marrow derived MNCs were obtained from the posterior iliac bone, isolated, and approximately 10 million cells/kg were administered intravenously within 72 hours of onset. The NIHSS scores at baseline and during follow up visits were recorded, and the total NIHSS and language scores were further evaluated in this study. FA and MD matrices were calculated using FSL Software

(FMRI, University of Oxford) by manually drawing a region of interest (ROI) on both the ipsilesional and contralesional AF.

**Results:** Four men and seven women with an average age of  $58.3 \pm 15.0$  years (age range 35-78 years) and a baseline infarct volume of  $62.2 \pm 60.0$  cc were evaluated in this study. The median NIHSS baseline total score was 14 (language range 1-3) and dropped to 2 (language range 0-2) at 24 months. The mean FA value on the ipsilesional AF was significantly lower ( $P < 0.05$ ) compared to the contralesional AF at all of the time points. The mean ipsilesional MD was significantly higher ( $P < 0.05$ ) at 6, 12, and 24 months compared to the contralesional AF. No dynamic changes in FA and MD were recorded on either the ipsilesional or contralesional AF.

**Conclusion:** A significant decrease in the mean FA on the ipsilesional AF strongly suggests that neuroimaging biomarkers can be used to assess the integrity of the AF tracts after an injury. There were no dynamic trend changes for FA values on the ipsilesional AF due to intra-patient variance. Furthermore, no changes in both the FA and MD on the contralesional AF support validation of this method. It is premature to conclude the effects of the cellular intervention; however, this should be further explored in future studies.

## ABSTRACT

### Angiotensin II Upregulates Mineralocorticoid Receptor Expression in Distal Nephron

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Key Words: Mineralocorticoid Receptors, Distal Nephron, Renin-Angiotensin-Aldosterone-System, Epithelial Na<sup>+</sup> Channel

**Background:** Hypertension affects approximately 26% of the world's population and greatly increases risk for stroke, heart disease, and renal failure. The kidneys are essential for setting and maintaining blood pressure (BP) via control of urinary sodium excretion. The epithelial Na<sup>+</sup> channel (ENaC) is of clinical importance for the development of strategies to aid in BP regulation, as it determines the rate-limiting step of Na<sup>+</sup> reabsorption in the distal nephron. ENaC is under stimulatory control by the renin-angiotensin-aldosterone system (RAAS). Angiotensin II (Ang II) stimulates ENaC via aldosterone-dependent and -independent pathways. Ang II is known to act on AT1 receptors of the adrenal zona glomerulosa to trigger release of aldosterone, which then acts to increase ENaC activity through binding to mineralocorticoid receptors (MR). Whether Ang II also coordinately upregulates MR is unknown. This study was designed to test the hypothesis that Ang II upregulates MR expression in the distal nephron and thereby contributes to upregulation of ENaC activity.

**Methods:** Wild type mice and those genetically lacking AT1 receptors were used to determine if Ang II signaling effects the expression of MR in the distal nephron. The mice were fed a Na<sup>+</sup> restricted or a high K<sup>+</sup> diet for 7 days to elicit differential responses of aldosterone and Ang II. After euthanization with CO<sub>2</sub>, the kidneys were harvested, homogenized, and protein extracts prepared. Protein amounts were quantified with the Bradford Protein Assay, and MR protein levels were quantified by Western Blotting. Anti-MR IgG Rabbit and Anti-Actin IgG Rabbit were used as primary antibodies, with Anti-Rabbit IgG-HRP as secondary antibodies for visualization. Protein bands were analyzed using Image Studio Lite and Origin 5.0 software followed by one-way ANOVA analysis, with a p-value of 0.05.

**Results:** Dietary Na<sup>+</sup> restriction, which causes elevation of both aldosterone and Ang II, significantly increases MR expression in whole kidney homogenates. In contrast, mice fed a high K<sup>+</sup> diet, which elevates aldosterone levels alone, failed to increase MR expression in the kidney. Moreover, genetic ablation of AT1 receptors drastically decreased MR expression at all tested dietary conditions. We conclude that Ang II controls ENaC activity, in part, by altering MR expression in the distal nephron.

## ABSTRACT

### Long Term TLR2 Stimulation does not Significantly Alter FVIII-Specific Immune Response

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Key Words: Hemophilia, TLR2, TLR4, T cells, FVIII

Hemophilia A, a genetic deficiency in deficient in clotting factor VIII (FVIII), results in excessive bleeding at sites of surgery or trauma. It has a prevalence of 1:5000 male births and has a worldwide distribution that affects all ethnic and racial groups (2). Patients with hemophilia A and bleeding episodes are treated by infusion of recombinant FVIII. However, up to 30% of these patients produce anti-FVIII inhibitor antibodies that bind to and functionally inactivate FVIII, thus rendering the replacement treatment ineffective (2). Current treatment for inhibitor antibody attempts to induce tolerance via massive doses of FVIII in combination with immunosuppression. Unfortunately, this therapy is costly (~\$900,000/patient) and fails in approximately 30% of patients. A more effective therapy would be to prevent inhibitor formation in the first place. It is known that production of inhibitor antibodies requires help from T cells. Dendritic cells (DCs) play an integral role in processing and presenting FVIII to T cells. The activation state of DCs is determined by signals through innate immune receptors, including the toll-like receptors (TLRs). Previous work in our laboratory suggested that repeated TLR2 stimulation did not affect inhibitor antibody formation, in contrast to repeated TLR4 stimulation, which significantly increased inhibitor antibody. To understand the immune mechanisms behind this, we investigated the effect of repeated TLR2 stimulation on antigen presenting cell and T cell recall response to FVIII. Factor VIII-deficient (FVIII-KO) mice were injected with recombinant human FVIII +/- TLR2 agonist (Pam(3)Cys). After 4 doses, splenocytes were isolated, re-stimulated with FVIII, and production of the inflammatory cytokines IL-6 and TNF- $\alpha$  was determined via ELISA. To ascertain the effects of repeated TLR2 stimulation on T helper cell response, T cells isolated from mice that received either FVIII, or FVIII + TLR2 stimulation were co-cultured with bone-marrow derived DCs and production of Th1 (IFN $\gamma$ ) and Th2 (IL-4) associated cytokines was measured. Our results showed that repeated stimulation with TLR2 resulted in increased production of IL-6 and TNF- $\alpha$ . However, this increase in inflammation did not correlate with changes in IFN- $\gamma$  secretion by antigen-experienced T cells, nor was it associated with increased T regulatory cells (Treg). In fact, increased percentage of Treg correlated with higher numbers of FVIII-specific antibody producing cells, regardless of TLR treatment. These results demonstrate that TLR2 stimulation drives a late inflammatory anti-FVIII immune response, but does not significantly modify downstream T cell and B cell activation. The specific effects of TLR2 stimulation on antigen-presenting cells, as well as differences in immune response among individuals as observed in this study need to be explored further. Additional investigation of downstream signaling pathways triggered by TLR2 and FVIII stimulation will shed more light on potential therapies to modify immune responses to therapeutic FVIII.



## ABSTRACT

### Effect of Surfactant Protein-A Dosage on Rat Models of Necrotizing Enterocolitis

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Key Words: NEC, SP-A

**Background:** Necrotizing enterocolitis (NEC) is the most serious gastrointestinal complication associated with preterm infants, resulting in the destruction of all or part of the bowel. NEC is associated with increased intestinal inflammation resulting from interactions of the lipopolysaccharides of bacterial pathogens interacting with the TLR4 receptors in the immature intestine, hypoxia of the developing intestine and enteral formula feeding. While there are no effective treatments after onset of NEC aside from surgery, we have found that pulmonary surfactant protein-A (SP-A) can ameliorate symptoms in animal models of NEC. My goal was to determine if SP-A has a dose-dependent effect to reduce NEC pathogenesis in a rat pup model of NEC.

**Methods:** Rat pups were separated from dams 2-3 days after birth and housed in an incubator. They were then assigned to different treatment groups and: Dam Fed, Formula Fed (100-150  $\mu$ l 4 times daily), Formula Fed with Hypoxia treatment (5% O<sub>2</sub>, 95% N<sub>2</sub> three times daily to induce experimental NEC) and Formula Fed with Hypoxia treatment with various amounts of SP-A (1 $\mu$ g - 15  $\mu$ g per pup per day). After the third day of feeding, about 5cm of the ileum was harvested for histological assessment of NEC and cytokine analysis by ELISA.

**Results:** Previously, formula plus hypoxia treatment resulted in 67% percent of animals getting NEC. In our investigations, 80% of the rats that were administered 1  $\mu$ g of SP-A developed NEC, 43% of the rats that were administered 10  $\mu$ g of SP-A developed NEC, and only 38% of the rats that were administered 15  $\mu$ g of SP-A developed NEC. The data indicates that a higher dosage is optimal. Cytokine analysis varied among the four trials and was inconsistent with the NEC scoring. TNF- $\alpha$  concentrations were lowest in rats administered 15  $\mu$ g of SP-A (2.39 pg/ml), which supports the statement that higher concentrations of SP-A are optimal. However, IL1- $\beta$  concentrations were higher in the 15  $\mu$ g SP-A dosage (22.9 pg/ml) than in the 10  $\mu$ g dosage (6.9 pg/ml).

**Conclusion:** While our data suggests that the incidence of experimental NEC decreases with oral administration of increased amounts of SP-A, associated changes in intestinal inflammatory cytokines were inconsistent and unexpected.

## ABSTRACT

### Increased Communication with Implementation of Post Anesthesia Care Unit (PACU) Checklist

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Supported by: The University of Texas Medical School at Houston – Office of the Dean

Key Words: Checklist, handoff, communication, post anesthesia care unit (PACU)

**Background:** Ineffective communication between clinicians has been found to lead to an increase in medical errors and a decrease in patient satisfaction. Effective communication should occur during handoffs in the post anesthesia care unit (PACU) where hundreds of transfers occur daily. This high turnover of patients makes it important to implement a handoff tool that reduces the amount of missed communication. Checklists provide structure and ensure that all pertinent patient information is communicated. Prior to this quality improvement study, there was no existing protocol for a handoff from the anesthesia team to the pediatric PACU nurses. We developed and implemented a meaningful checklist to standardize this communication process.

**Methods:** During the first two weeks of the project, we observed handoffs and audited according to a published checklist (pre-education phase). After data review, a checklist adapted specifically for the pediatric PACU was developed using input from the nursing staff and pediatric anesthesiologists. The checklist was placed above beds in the PACU and pocket size checklists were distributed to pediatric anesthesia care providers. An email was sent out informing the pediatric anesthesia providers of the new checklist that was to be implemented during handoffs. During the following week, we educated on how to use the checklist and informed about missed points (education phase). Another re-enforcing email was sent out after a week of education because it was noted that there were some anesthesia providers who were not complying with the checklist. We audited the success of our implementation the following week (post-education phase).

**Results:** The reliability of handoffs improved from 2% to 69% with the introduction of a standardized checklist. A total of 150 handoffs were observed over a four-week period distributed over three study phases: pre education, education, and post education. Prior to any formal checklist, only one report out of the 50 observed during the pre education phase was given perfectly (2%). To be qualified as perfect all points of the published checklist had to be addressed. After introduction of the new handoff protocol, 31% of handoffs were done perfectly during education week. The most missed item was the weight of the patient, which improved from 26% during pre education to 84% post education.

**Conclusion:** Adherence to the checklist increased the communication occurring between the anesthesia team and PACU nurses. It allowed for nurses to get the pertinent patient information in an organized manner. In order to achieve our goal of 100% adherence, more education for anesthesia providers is needed. Another audit will be conducted in a month to follow up on checklist adherence.

## **ABSTRACT**

### **Preventing Post-Traumatic Stress Disorder: Translating Endocrine and Behavioral Correlates of Disease from Mice to Humans**

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Sponsored by: Nicholas Justice, PhD, Institute of Molecular Medicine

Supported by: Nicholas Justice, PhD, Institute of Molecular Medicine, and Mr. Ralph O'Connor

Key Words: PTSD, prevention, HPA axis, mouse model

Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder characterized by intrusive memories, hyperarousal, and avoidance of trauma related cues. A diagnosis of chronic PTSD is made at least three months after a traumatic event. During the first three months post-trauma, aberrant activity of the hypothalamic-pituitary-adrenal axis (HPA axis) is thought to be involved in the development of chronic PTSD. Many studies suggest that hyper-activity of the HPA axis during this critical period, particularly elevated release of Corticotropin releasing factor (CRF), causes PTSD, while others suggest that insufficient HPA axis activity during the critical period subsequently leads to PTSD. Here, we used a mouse model of PTSD to examine whether pharmacologic restoration of normal HPA axis activity during a critical period after trauma exposure influences later development of a PTSD-like phenotype. We found that exposure to high-intensity trauma generates a PTSD model in mice; mice exhibit a constellation of behavioral and endocrine PTSD-like symptoms after a critical period of one week following trauma exposure. When we treated animals that underwent PTSD-like induction with corticosterone to mimic activation of the HPA axis, this exaggerated the PTSD-like phenotypic profile while chronically decreasing HPA axis activity. When we inhibited the HPA axis using CRFR1 antagonists, we observed a mild, non-statistically significant abrogation of PTSD-like behavioral symptoms. Together, these experiments show that manipulation of the HPA axis during a critical period after trauma exposure can affect chronic development of PTSD-like phenotypes in mice. Parallel studies in humans were focused on establishing baseline parameters for measuring eye blink in response to a 110dB acoustic startle, for use as a biomarker of PTSD severity. The results indicate that men have a higher startle magnitude than women. In addition, men exhibit greater prepulse inhibition at lower prepulse intensities than women. With human studies of factors that influence PTSD development and mouse experiments testing the dependence of PTSD on HPA axis activity characteristics, we hope to identify pharmacologic means of preventing or attenuating PTSD in the clinic.

## ABSTRACT

### Learner Perceptions of Online Education in Anesthesiology: An Analysis of Methodological Issues and Development of Strategies to Enhance the Delivery of Knowledge

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Supported by: Paul G. Loubser, MD, Department of Anesthesiology

Key Words: asynchronous education

**Background:** The growing field of online education has enormous potential to enhance the students' education with a personalized experience. Asynchronous education is a form of online education that allows students to utilize learning resources at their own pace, while synchronous education occurs at the same time online. The Department of Anesthesiology at the Memorial Hermann Heart & Vascular Institute-Texas Medical Center developed an asynchronous learning website, Online Resource in Cardiac Anesthesia (O.R.C.A.), with the goal of supplementing the anesthesia residents' education. The purpose of this study was to determine the perceptions of O.R.C.A., of online education in general, and of possible barriers to asynchronous education.

**Methods:** Of seventy-one residents given access to O.R.C.A., thirty-four (47.9%) logged into the website (users). We designed an online ten-question survey to assess the users' feedback. Additionally, a different online survey was created for the thirty-five residents who did not access the website (non-users) to determine their reasons for not logging into O.R.C.A.

**Results:** The survey's response rate was 41.2% (14/34) and 32.4% (12/37) for the users and non-users, respectively. Of the users, the majority found the website useful in enhancing their education in the operating room (79%) and in building their knowledge of cardiac anesthesia (93%). 100% of users surveyed preferred online education integrated into their traditional education, either predominantly (50%) or as an equal mix with traditional education (50%). Visual learning tools such as videos, images, and presentations were strongly preferred by the users over other learning tools such as audio or articles. While 55.6% of non-users did not prefer a different mode of education than online learning, 66.7% claimed they did not have enough time to utilize O.R.C.A. or had technological issues (33.3%).

**Conclusion:** Results from this study indicate that anesthesia residents can receive enhanced education and expanded knowledge by using online learning tools. While the majority of residents surveyed prefer a learning model that includes online education, roughly half of the residents did not use the O.R.C.A. website. Barriers to asynchronous education still remain and should be addressed in further research. The development of strategies to remove such barriers such as integrating synchronous education or the use of preferred visual learning tools could motivate the students' use of online learning tools.

# ABSTRACT

## Trends in 1029 Trauma Deaths at a Level 1 Trauma Center

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Supported by: John B. Holcomb, MD, Department of Surgery, Center for Translational Injury Research; The University of Texas Medical School at Houston – Office of the Dean

Key Words: Trauma, Trauma Death

**Introduction:** Over the last decade the age of trauma patients and injury mortality has increased. At the same time, we have implemented many interventions focused on improved hemorrhage control. The objective of our study was to analyze the temporal distribution of trauma-related deaths, the factors that characterize that distribution and how those factors have changed over time at our level 1 trauma center.

**Methods:** The trauma registry, weekly Morbidity & Mortality reports and electronic medical records at Memorial Hermann Hospital in Houston, TX were reviewed. Patients with primary burn injuries and pediatric age (<16) patients were excluded. Two time periods (2005-2006 and 2012-2013) were included in the analysis. Baseline characteristics, time and cause of death were recorded. Mortality rates were directly adjusted for age, gender and mechanism of injury. Results are expressed comparing 2005-2006 with 2012-2013. The Mann-Whitney and chi square tests were used to compare variables between periods, with significance set at the 0.05 level.

**Results:** 7080 patients including 498 deaths were examined in the early time period, while 8767 patients including 531 deaths were reviewed in the recent period. The median age increased 6 years between the two groups, with a similar increase in those who died, 46 (28-67) to 53 (32-73) ( $p<0.01$ ) years. In patients that died, no differences by gender, race or ethnicity were observed. Fall-related deaths increased from 20% to 28% ( $p<0.01$ ) while deaths due to motor vehicle collisions decreased from 39% to 25% ( $p<0.01$ ). Deaths associated with hemorrhage decreased from 36% to 25% ( $p<0.01$ ). 26% of all deaths (including dead on arrival, DOAs) occurred within one hour of hospital arrival, while 59% occurred within 24 hours, and were similar across time periods. Unadjusted overall mortality dropped from 7.0% to 6.1% ( $p=0.01$ ) and in-hospital mortality (excluding DOA) dropped from 6.0% to 5.0% ( $p<0.01$ ). Adjusted overall mortality dropped 24% from 7.6% (95% CI: 6.9-8.2) to 5.8% (95% CI: 5.3-6.3) and in-hospital mortality decreased 30% from 6.6% (95% CI: 6.0-7.2) to 4.7% (95% CI: 4.2-5.1).

**Conclusions:** Although US data show a 20% increase in death rate due to trauma over a similar time period, this single-site study demonstrated a significant reduction in adjusted overall and in-hospital mortality. It is possible that concentrated efforts on improving resuscitation and multiple other hemorrhage control interventions resulted in the observed reduction in hemorrhage related mortality. Most trauma deaths continue to be concentrated very soon after injury. We observed an aging trauma population and an increase in deaths due to falls. These changing factors provide guidance on potential future prevention and intervention efforts.

## ABSTRACT

### Prognosis, Prevalence and Characteristics of Lactate Expressors and Non-expressors in Severe Sepsis and Septic Shock

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Sponsored by: Pratik Doshi, MD, Department of Emergency Medicine

Supported by: Pratik Doshi, MD, Department of Emergency Medicine; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Severe sepsis, septic shock, lactate

**Introduction:** Severe sepsis and septic shock cause significant morbidity and mortality among all patient demographics. In 1995, there were more than 750,000 cases of severe sepsis and septic shock within the United States, and since then, this number has grown an estimated 13% each year. Initial early recognition, with timely antibiotics and aggressive resuscitation focusing on physiologic endpoints, has been shown to improve mortality in this cohort. A specific physiologic endpoint targeted in this cohort is lactate level, and multiple studies have shown lactate to be independently associated with mortality in this group. However, not all patients express lactate despite having acute organ dysfunction or hypotension in the setting of sepsis. There is very limited evaluation of the prevalence of these patients and their outcomes.

In this study, we sought to examine the prevalence and outcomes of lactate expressors versus lactate non-expressors in a cohort of patients presenting with severe sepsis or septic shock.

**Methods:** A retrospective chart review was performed of patients admitted to Memorial Hermann Hospital with the diagnosis of sepsis or an infection with associated organ dysfunction between October 1<sup>st</sup>, 2010 and December 31<sup>st</sup>, 2013. Source of infection, initial serum lactate value, escalation of care, ICU length of stay, hospital length of stay, mortality and factors included in the calculation of the Acute Physiology and Chronic Health Evaluation (APACHE II) score were all recorded. Patients were categorized as “lactate expressor” if their initial lactate was  $\geq 2.5$ , and as “lactate non-expressor” if their initial lactate was  $< 2.5$ . In addition, the patients were divided into severe sepsis versus septic shock based on whether patient had hypotension, defined as SBP  $< 90$ , despite adequate fluid resuscitation.

**Results:** A total of 1004 records met the criteria for the initial search. 351 records had a lactate level drawn at presentation, of these 338 met the definition of severe sepsis or septic shock and were included in the final analysis. 197(58%) patients were lactate expressors and 141(42%) were lactate non-expressors. Unadjusted mortality was 45% and 19% in the lactate expressor and lactate non-expressor groups, respectively. 160 records met criteria for severe sepsis and remaining 178 met criteria for septic shock. 50% and 35% were lactate non-expressors in the severe sepsis and septic shock groups, respectively. Lactate expressors in both groups had higher severity of illness scores which was statistically significant. Unadjusted mortality was 39.5% and 22.8% ( $p=0.02$ ) in the severe sepsis group when divided into lactate expressor and lactate non-expressor groups, respectively. Unadjusted mortality was 50.9% and 27.4%  $p=0.002$

in the septic shock group when divided into lactate expressor and lactate non-expressor groups, respectively. There were no statistically significant differences in ICU or hospital Length of stay between these groups. Escalation of care within 24 hours of initial hospital admission happened more frequently (16.5% vs 6.2%,  $p=0.04$ ) in severe sepsis group who were lactate non-expressors.

**Conclusions:** Lactate non-expressors represent a large proportion of patients presenting with severe sepsis and septic shock, and although they represent a group with lower severity of illness and mortality when compared to lactate expressors, they still carry a significant mortality burden and should have the same requirement of early recognition and resuscitation as is suggested by surviving sepsis guidelines.

## **ABSTRACT**

### **Lipophagy Reverses Lipid Accumulation in Rat L6 Myocytes**

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Supported by: National Institute of Diabetes and Digestive and Kidney Disease,  
2T35DK007676-21A1

Key Words: Autophagy, Lipids, Skeletal Muscle

Lipid accumulation in non-adipose tissues, such as skeletal and cardiac muscle, leads to maladaptive effects and organ effects in obese patients. Weight loss induced by bariatric surgery promotes a loss of this excess lipid in skeletal and cardiac muscle at three and nine months post-surgery, however, the mechanisms underlying this phenomenon are unknown. We hypothesized that autophagy of lipids --- lipophagy ---mediates the reversal of intramuscular lipid accumulation and protects the skeletal muscle cell from lipotoxicity, cell death and dysfunction from excess lipid accumulation. Autophagy is a catabolic mechanism that results in the intracellular degradation of dysfunctional cellular components through lysosomes. To test this hypothesis, L6 myocytes (rat skeletal muscle cells) were treated with both saturated and unsaturated fats ( 1.0 mM equimolar palmitate and oleate, respectively) to simulate chronic lipid overload, then administered an inducer (rapamycin, 1  $\mu$ M) or inhibitor (bafilomycin A1, 200 nM) of autophagy, or a combination of both. Immunoblotting with antibodies for p62 and LC3, and apoptosis with Caspase-3, were performed to confirm changes in autophagic flux . Oil Red O staining and direct quantification with an enzymatic assay were used to determine intracellular triglyceride (TG) accumulation. Our previous work established that rapamycin-induced autophagy leads to clearance of lipid accumulation in myocytes L6 cells. In the present study, L6 cells treated with a combination of rapamycin and bafilomycin yielded unexpected findings. Despite bafilomycin inhibition, cells treated with this combination still underwent autophagy. Through immunofluorescence and immunoblotting, we confirmed that autophagy still proceeded through an alternative pathway. To make sure this was not the result of rapamycin being an incomplete inhibitor of mTOR, we used Torin1, a complete inhibitor of mTOR, to determine whether the results of rapamycin + bafilomycin treatment could be duplicated. Autophagic flux was observed for Torin1 at 24 and 48 hours as measured by increased LC3 and decreased p62 levels. Combination treatment with Torin1 and bafilomycin resulted in decreased autophagy, which contrasts with the combination treatment with rapamycin and bafilomycin. These results suggest that the alternative pathway we noticed was a side effect of rapamycin treatment, and not a consequence of altered autophagy. Our next experiments include staggering treatments of bafilomycin and rapamycin to determine if rapamycin can not only induce autophagy to clear lipids, but is capable of reversing lipotoxicity induced by bafilomycin. We will also look more closely at how lipophagy alters metabolism by measuring glucose versus fatty acid oxidation with radioactive tracers.



## ABSTRACT

### Impact of Tranexamic Acid (TXA) on Mortality of Trauma Patients with Hyperfibrinolysis

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Sponsored by: John A. Harvin, MD, Bryan A. Cotton, MD, MPH, John B. Holcomb, MD, CeTIR

Supported by: The Center for Translational Injury Research; The University of Texas Medical School at Houston—Office of the Dean

Key Words: Tranexamic Acid, Hyperfibrinolysis, Hemorrhage, Mortality

**Background:** Hemorrhage is the leading cause of death among trauma patients in the first 24 hours. The coagulopathy associated with post traumatic hemorrhage is associated with increased mortality. One mechanism of post traumatic coagulopathy is the pathologic degradation of clot - hyperfibrinolysis. Thromboelastography (TEG) can measure hyperfibrinolysis; specifically, the percent clot lysis at 30 minutes (LY30) quantifies the degree of clot degradation. A 2011 study performed at MHH-TMC defined hyperfibrinolysis as LY30 >3%. Tranexamic acid (TXA) is a lysine derivative that prevents plasmin activation by blocking plasminogen/fibrin interaction. A randomized, placebo-controlled trial published in 2010 showed that administration of TXA within 32 hours of injury was associated with decreased mortality. Conversely, TXA administration given after three hours from injury was associated with increased mortality. Methodological limitations of that study prevented it from being applicable at MHH-TMC. However, a data-driven protocol using the LY30 to determine TXA administration was adopted in July 2011. It states that TXA should be administered to bleeding patients with LY30 values >3% within three hours of the initial injury. This study aims to determine the impact on mortality of administering TXA to bleeding patients.

**Methods:** Following IRB approval, a retrospective analysis of all trauma patient >15 years of age and with an admission LY30 >3% admitted to MHH-TMC between August 2009 to September 2013 was performed. Patients were then divided into those who received TXA and those who did not. Outcomes include death, transfusions, thrombotic events, and other complications (pneumonia, ARDS). Univariate and multivariate analysis were performed. A logistic regression model was developed *a priori* to evaluate the impact of TXA on in-hospital mortality (controlling for age, gender, ISS, and arrival physiology).

**Results:** 1,302 patient met inclusion criteria - 98 received TXA and 934 did not. As expected, the patients who received TXA were more severely injured (median ISS 29 vs 14,  $p < 0.001$ ), more hypotensive (median SBP 103 vs 125,  $p < 0.001$ ), and were more likely to be in shock (median BE -5 vs -2,  $p < 0.001$ ). In the TXA group, all values on the TEG were more hypocoagulable, including ACT, alpha angle, maximum amplitude, and LY30. Unadjusted mortality was higher in the TXA group (34% vs 10%,  $p < 0.001$ ). Unadjusted rates of transfusions, pneumonia, sepsis, and decubitus ulcers were higher in the TXA group.

Controlling for age, gender, ISS, mechanism of injury, SBP, and base excess, no difference in in-hospital mortality was associated with TXA administration. After similar controlling, however, TXA administration was associated with an increase in 24 hour mortality.

**Discussion:** Administration of TXA was not associated with increased in-hospital mortality but was associated with increased 24-hour mortality even when adjusted for severity of injury. Additionally, the administration was not associated with reversal of LY30 to < 3%. These results suggest that the potential benefit conferred by TXA in the 2010 trial may not be applicable to a mature, Level 1 trauma center.

## ABSTRACT

### Assessment of Possible Chromosomal Instability of a Novel Population of Stem Cells

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Sponsored by: Yong Li, MD, PhD, Department of Pediatric Surgery

Supported by: Department of Pediatric Surgery

Key Words: Chromosome, karyotype, cytogenetics, muscle stem cells

Numerical and structural chromosomal aberrations of stem cells (SCs) are of significant scientific interest, since proving that SCs have a normal and stable karyotype is a crucial quality control criterion when applying SCs in the clinic. In recent years, this lab has worked extensively with adult muscle stem cells. Recently, the lab identified a novel population of dedifferentiated muscle SCs (deMuSCs) which have unique features and can provide an alternative cell source for tissue regeneration, especially in neural-muscle related injuries and diseases. In order to prove the relevance of these cells for future therapeutic applications, assessment of genomic stability is vital. Using conventional cytogenetic methods, we analyzed the karyotypes of the deMuSCs to assess their health and genomic stability. Myoblasts originating from mice with the *Loxp* gene were found to be normal 40,XY, indicating a stable genome. In contrast, a subpopulation of primary myoblasts in which the *Cre* gene was transferred into showed an abnormal female karyotype, indicating genomic instability. Both the *Cre* and the *Loxp* cell lines were analyzed at passage twelve. Further evaluation of additional subpopulations of *Cre* clonal cells is ongoing. We will also evaluate muscle-derived cells from genetically engineered *Cre* mice (B6.Cg-Tg (ACTA1-cre)<sup>79Jme</sup>/J, Jackson Laboratory) as well as investigate additional various *Loxp* cells to further assess genomic stability. Analysis of cells following the fusion of *Cre* and *Loxp* cells revealed a karyotype of 41,XX,+5, possibly due to the high number of passages (19). Finally, cells were isolated from MDX-SCID mice and sorted for *LacZ*<sup>+</sup> cells indicating successful *Cre-Loxp* fusion. Chromosome analysis of these cells showed a normal 40,XY karyotype. Experiments are currently being repeated to maintain gender consistency as well as to reassess karyotypes at earlier passages, since later passages are known to induce chromosomal abnormalities.

## **ABSTRACT**

### **Exploring a Possible mechanism for Aspirin and Aspirin-PC's Therapeutic Effect in Cancer.**

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Sponsored by: Lenard M. Lichtenberger, PhD, Department of Integrative Biology and Pharmacology

Supported by: National Institute of Diabetes and Digestive and Kidney Disease, 2T35DK007676-21A1

Key Words: Cancer, aspirin, aspirin-PC

Non-steroidal anti-inflammatory drugs (NSAIDs) act through the inhibition of cyclooxygenase (COX) -1 and -2 enzymes and are primarily used to reduce pain and inflammation. However observational studies have shown NSAIDs, such as aspirin, reduce the incidence and metastasis of certain types of cancer, although the mechanism of this therapeutic action is unknown. Unfortunately the long term use of aspirin has shown to damage the gut. The damaging effect to the gut can be attenuated through the pre-association of aspirin with soy phosphatidylcholine (PC). In addition, evidence shows that aspirin-PC can be more effective in preventing the progression of cancer as shown in rat models. Our hypothesis is that aspirin-PC will have a greater affinity to localize to cancerous tissue than aspirin.

In this study, BALB/C mice were injected with MC-26 cancer cells into their spleen. The mice were then separated into three groups and orally administered daily with normal saline solution, 20 mg/kg aspirin, or 20 mg/kg aspirin-PC. After four weeks of this treatment, the mice were sacrificed and their spleen, ileum, and liver were harvested. The tissue samples were analyzed using high performance liquid chromatography to determine the amount of aspirin and its end product salicylic acid present in the tissue.

Mice treated with Aspirin-PC displayed an increased trend of salicylic acid (SA) in spleen tissue, with a mean of  $0.96 \mu\text{g} \pm 0.42 \text{ SA/g tissue}$  as opposed to mice treated with unmodified aspirin that displayed  $0.26 \mu\text{g} \pm 0.05 \text{ SA/g tissue}$ . In addition, mice treated with aspirin-PC showed a decreased trend of SA in the liver and ileum in respect to aspirin treated mice. Although statistical significance was not reached, this data provides evidence that aspirin-PC has a greater affinity to specifically localize to cancerous tissue than aspirin.

## ABSTRACT

### Variability in Surgical Skin Preparation Adherence in Common Pediatric Operations

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Sponsored by: KuoJen Tsao, MD, Department of Pediatric Surgery

Supported by: KuoJen Tsao, MD, Department of Pediatric Surgery

Key Words: Surgical skin prep, chlorhexidine gluconate, povidone-iodine

**Overview and Significance:** Skin antiseptics are used for preoperative preparation to decrease surgical site infections. However, surgeon preference, anatomical site considerations, and patient age may influence proper agent utilized. Despite evidence-based guidelines, we hypothesized that adherence to skin preparation guidelines is variable in pediatric operations.

**Methods:** A retrospective cohort study of eight common pediatric operations was performed to evaluate skin prep agent utilized over a one year period. Operations included: laparoscopic appendectomy, fundoplication, gastrostomy tube placements, pyloromyotomy, laparoscopic cholecystectomy, abscess incision and drainage, inguinal hernia repair, and stoma takedown. Up to 25 cases of each operation were reviewed. The skin prep used for each operation was recorded as well as patient age (younger/older than 6 weeks), gender, operative time, prep nurse (if circulated  $\geq 10$  operations), surgeon, and anatomical site of prep (torso, extremity, pelvis/perineum). Proper agent was determined to adherence to our institutional guidelines. Logistic regression and the chi squared test were performed;  $p < 0.05$  were considered significant.

**Results:** A total of 183 cases were reviewed with an overall adherence of 58% to skin prep guidelines. Adherence to skin prep guidelines was highest for laparoscopic cholecystectomies and laparoscopic appendectomies (96% and 92%, respectively) and lowest for stoma takedowns and inguinal hernia repairs (8% and 32%, respectively). In addition to operation, the variability in skin prep adherence was significantly different based on the surgeon and patient age (all  $p < 0.05$ ).

**Conclusion:** Significant variability in adherence to correct skin prep guidelines exists for common pediatric operations. Contributing factors include type of operation, surgeon, and patient's age. Consistent practice and adherence to evidence-based guidelines for skin preparation requires targeted interventions in these areas in order to improve overall adherence.

## **ABSTRACT**

### **Evaluation of a Respiratory Monitor in Surgical Patients with a BMI >35 Undergoing Elective Surgery under General Anesthesia**

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Supported by: Evan Pivalizza, MD, Department of Anesthesiology; The University of Texas Medical School at Houston – Office of the Dean

Key Words: Obstructive Sleep Apnea (OSA)

The accurate assessment of respiratory parameters in nonintubated patients during the post-operative period is important and continues to be a challenge despite technological advances. Respiratory depression and other complications are likely to occur during this recovery period due to residual anesthetics. Patients with an existing co-morbidity such as obesity are at a much higher risk for undergoing these post-operative respiratory complications. Currently, assessment of respiratory status in nonintubated patients relies on measurements such as pulse oximetry, spirometry, respiratory rate sensors, CO<sub>2</sub> monitoring, and clinical assessment. While these techniques have proved to be valuable, they do not provide real-time measurements and are unfortunately late indicators of respiratory stress. A noninvasive Respiratory Volume Monitor (RVM) has recently been developed, which allows for accurate, continuous, real-time measurements of tidal volume (TV), respiratory rate (RR), and minute volume (MV). This device has the potential utility in providing early detection of respiratory decline so that interventions can be implemented in a timely manner. Previous studies have indicated the clinical relevance of the RVM in the general population, but none have examined the obese population specifically.

The purpose of this study was to evaluate the utility of this device by comparing the respiratory measurements obtained from this device to those obtained from the ventilator in the operating room. In order to evaluate the RVM, consent was obtained from healthy adults undergoing elective surgery under general anesthesia with a BMI greater than 35 kg/m<sup>2</sup>. An adhesive PadSet was placed on the patient's chest prior to surgery that allowed the RVM to measure respiratory parameters. A STOP-Bang questionnaire (to assess the patient's risk of obstructive sleep apnea) was given to the patient and spirometry testing was performed. Data was then continuously gathered for the remainder of the pre-operative period, throughout surgery, as well as during the post-operative period until the patient met the discharge criteria from the PACU. During a ten-week period, 30 subjects participated in the study. Because this is an ongoing study (anticipated enrollment of 100 subjects), data analysis has not yet been completed. In conclusion, further analysis will be done once the subject enrollment becomes larger. The data collected from this device will also be used to determine the correlation between apnea episodes that are detected by the device and the subject's risk for sleep apnea. The data obtained through this study will help improve the safety of patients and help health care providers predict early signs or respiratory decline and prevent complications.

## **ABSTRACT**

### **Management of Median Arcuate Ligament Syndrome, Median Follow-up, and a Review of Literature**

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Sponsored by: Ali Azizzadeh, MD, Department of Cardiothoracic and Vascular Surgery

Supported by: The University of Texas Medical School at Houston – Office of the Dean

Key Words: Median Arcuate Ligament Syndrome, Celiac Artery Compression

**Background:** Median Arcuate Ligament Syndrome (MALS) is a condition of celiac artery compression by the median arcuate ligament, most often associated with chronic abdominal pain.

**Methods:** We collected retrospective data from our hospital and clinic registry for patients who underwent celiac artery decompression surgery in the past 5 years. We contacted all 8 patients and completed the SF 12 quality of life survey. We updated a previous review of literature (Jimenez) to include data published between 2012 and 2014. Also included was an analysis of the National Inpatient Sample (NIS) between 1999 and 2011.

**Results:** Five hundred and four patients underwent open or laparoscopic intervention for MALS, four hundred and sixteen of which reported immediate postoperative symptom relief (83%). Our series of eight patients, treated with open surgical decompression, reported complete immediate postoperative and late symptom relief (100%). Investigation of the NIS revealed that between 2000 and 2011, only 2.44% of patients diagnosed with MALS received decompression.

**Conclusions:** Both laparoscopic and open surgical treatment relieves symptoms for patients afflicted with MALS. Though laparoscopic surgery has become more predominant, we continue to report open intervention as a safe and effective treatment option for patients suffering celiac artery compression.

## **ABSTRACT**

### **The Effect of Incretin Based Therapies on Endothelial Dysfunction in Humans with Prediabetes**

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Sponsored by: Absalon Gutierrez, MD, Department of Internal Medicine, Division of Endocrinology, Diabetes, and Metabolism  
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Supported by: National Institute of Diabetes and Digestive and Kidney Disease, 2T35DK007676-21A1

Key Words: Prediabetes, endothelial dysfunction, cardiovascular disease

Tight glycemic control may not be optimal for improving cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM), and two-thirds of all deaths in diabetic patients are due to coronary heart disease. Prediabetic and T2DM patients have increased endothelial dysfunction. Coronary artery endothelial dysfunction correlates with decrease in forearm blood flow (a noninvasive measurement) after a high-fat meal. The glucagon-like peptide 1 receptor analogue (GLP-1RA), exenatide, was recently shown to improve postprandial endothelial dysfunction after a high-fat meal. The dipeptidyl peptidase -IV (DPP-IV) inhibitor, saxagliptin, targets the same signaling pathways which may yield similar effects. This project examined the efficacy of exenatide and saxagliptin in ameliorating endothelial dysfunction in humans with prediabetes. This is the beginning of a randomized, crossover, placebo-controlled, double blinded prospective trial with three study arms: placebo, exenatide, and saxagliptin. The subjects are prediabetic men and women ages 30-70 years with a BMI between 30-35 kg/m<sup>2</sup> and no confounding medical conditions or treatments. Subjects participate in 3 day-long visits, each representing one study arm (exenatide, saxagliptin, or placebo) with ≥10 day washout period between each visit. The study medication is given prior to a standardized high-fat meal. The primary outcome is change in forearm blood flow (in mL/min), a measured per noninvasive strain gauge venous occlusion plethysmography at baseline (prior to the meal) and 180 minutes after the meal. Preliminary data show an improvement in forearm blood flow in one of the study arms and that the entire study is feasible.



## ABSTRACT

### Near Perfect Checklist Adherence: Is There Still Room for Improvement?

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Supported by: KuoJen Tsao, MD

Key Words: Clinical/Outcomes, Clinical Trials/Outcomes, Patient Safety, Quality of Care, Perioperative Care

**Introduction:** Surgical safety checklists were created to maximize quality of care for every patient every time, but the checklists themselves may be meaningless if not followed appropriately. Observational data from Children's Memorial Hermann Hospital (CMHH) has demonstrated acceptable adherence to the pre-incision (timeout) checklist; however, there has been little research done to investigate operative characteristics that may further influence adherence to the checklist. We hypothesized that CMHH pre-incisional checklist adherence has significantly improved since its implementation, and that case complexity may influence checklist adherence.

**Methods:** From June 2011 to August 2014, adherence to CMHH's 14-point pre-incision checklist was directly assessed by trained observers during four distinct, 7-week periods separated by one year intervals (baseline, observation #1, observation #2, and observation #3). Checklist adherence was determined to be the median percentile of checkpoints completed per case. Factors that were hypothesized to potentially influence checklist adherence included: surgical specialty, case complexity, case duration, case start time, and timeout length. Case complexity was determined by the amount of relative-value-units (RVU) assigned to the case. Kruskal-Wallis, Spearman's rank correlation, and chi-squared analyses were performed;  $p < 0.05$  was considered significant.

**Results:** Execution of the pre-incision checklist was observed for 1,139 cases (baseline=144, observation #1=373, observation #2=356, observation #3=266). Overall adherence was found to have significantly increased over the study period (30% to 76% to 96% to 98%,  $p < 0.001$ ). The median (interquartile range) number of RVUs per case was 9.5 (4.9-18.5), median case duration was 43 (23-88) minutes, and median timeout length was 82 (68-115) seconds. Adherence did not differ significantly based on specialty, case complexity, case duration, case start time, or timeout length ( $p > 0.05$ ). However case complexity, as measured by RVU's, was associated with longer case duration and timeout length (both  $p < 0.001$ ).

**Conclusion:** Adherence to the pre-incisional checklist significantly improved from 30% to 98% over the course of four years. However, there does not appear to be a relationship between adherence and case complexity, timeout length, or case duration, perhaps suggesting that the checklist is not being carried out meaningfully, and with the appropriate amount of discussion and fidelity that more complex cases likely require. Further investigation of the quality of checklist execution is warranted.

## ABSTRACT

### **Influence of Metformin versus Placebo on Selected Biomarkers as Related to Postpartum Weight Loss in Women with Gestational Diabetes (GDM)**

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Sponsored by: Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP, Department of Obstetrics, Gynecology, and Reproductive Sciences

Supported by: Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP, Department of Obstetrics, Gynecology, and Reproductive Sciences; The University of Texas Medical School at Houston – Office of the Dean

Key Words: Metformin, weight-loss, postpartum, oxidized LDL, leptin, HDL, cardiovascular disease

**Introduction:** Obesity is associated with oxidative stress and inflammation. Excess gestational weight gain and inadequate postpartum weight loss can put women at the risk for developing obesity and secondary sequelae such as cardiovascular disease (CVD) and Type II Diabetes Mellitus (TIIDM). Metformin is a drug already used to improve carbohydrate tolerance, effective for TIIDM, and has been seen to decrease the risk of gestational diabetic women developing TIIDM later in life. It has also been seen to help with weight loss and decrease in lipid and cholesterol synthesis. Additional benefits of postpartum administration of metformin to women with GDM should include evaluation of biomarkers such as oxidized LDL (ox-LDL) - a marker of oxidative stress related inflammation and the risk of development of CVD, leptin- a hormone that suppresses appetite and associated with weight loss, and ghrelin- a hormone associated with stimulating food intake and associated with weight gain will provide.

**Specific Aim:** Evaluate the impact of metformin on obesity biomarkers leptin, ghrelin, insulin, glucose, ox-LDL, HDL, and total cholesterol. The hypothesis to be tested is whether metformin accelerates the rate of postpartum weight loss and influences levels of a specific biomarker(s) associated with obesity.

**Methods:** A secondary analysis of a randomized controlled trial (RCT) of metformin versus placebo in women with Blood samples were collected from 77 patients with history of gestational diabetes randomized to either metformin 850 mg once daily for seven days, then twice daily for five weeks (N=42) or placebo (N=35) immediately post-delivery and again six weeks later. Plasma was then assayed per the manufacturer's protocol for total cholesterol, HDL, ox-LDL, glucose, insulin, leptin, and ghrelin.

**Results:** There was no significant weight change between groups observed in the primary RCT.

In this analysis 91%(32/35) metformin group had no change or an increase in HDL compared to 85.7%(36/42) in the placebo group. 60%(21/35) metformin group had a decrease in ox-LDL compared to 38%(16/42) in placebo group. 83%(29/35) metformin group had an increase in leptin compared to 53%(23/42) in placebo group. There were minimal differences in glucose, insulin, or total cholesterol.

**Conclusion:** Although a significant weight loss was not observed, data suggest metformin stabilized of HDL, increased leptin associated with improved appetite suppression, and reduced in ox-LDL that suggest decrease oxidative-stress related inflammation. These improvements in biomarkers may facilitate ultimate weight loss and potentially decrease the risk of development of CVD with a longer duration of metformin.

## ABSTRACT

### Integrity of Neuronal Fibers in the Corpus Callosum of Ischemic Stroke Patients Treated with Autologous Bone Marrow Derived Mononuclear Cells

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Sponsored by: Sean I. Savitz, MD, Department of Neurology, Muhammad E. Haque, PhD,  
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Supported by: The University of Texas Medical School at Houston – Office of the Dean

Key Words: Diffusion Tensor Imaging, Ischemic Stroke, Stem Cells, Corpus Callosum

**Background:** Thrombolytic agents during the acute phase of stroke have been recognized as the only available treatment for selective groups of patients. Once the cellular damage has occurred, there is little that can be done to restore pre-stroke conditions. Damage to the corpus callosum (CC) prevents the relaying of sensory, motor, and cognitive information between the two cerebral hemispheres. Autologous bone marrow mononuclear cell (BM-MNC) transplantation as a possible alternative treatment for ischemic stroke is promising. The next phase of this investigational therapeutic requires quantifying efficacy and longitudinal monitoring for any possible side effects.

**Objective:** In this research we investigate the effects of stroke on the integrity of the CC fibers. The primary objective of this research was to develop neuroimaging makers that can quantify and characterize post therapeutic micro-structural fiber changes.

**Methodology:** We applied non-invasive diffusion tensor imaging (DTI), which uses water molecules' diffusion and direction as a tracer to provide information about microstructural properties of tissues. Fractional anisotropy (FA) and mean diffusivity (MD) are the two imaging matrices applied to evaluate the integrity of white matter and neuronal density, respectively. We enrolled 25 ischemic stroke patients treated with autologous BM-MNCs. Here we are presenting a subset of twelve patients who completed the serial imaging at all time points. Bone marrow was harvested aseptically from the posterior iliac bone and approximately 10 million cells/kg were administered IV. Total and motor National Institutes of Health Stroke Scale (NIHSS) and imaging data were obtained at 1, 3, 6, 12, and 24 months. Dynamic changes in DTI matrices were quantified using region of interest (ROI) and tract based analysis in the genu and splenium regions of the corpus callosum in both the ipsilesional and contralesional hemispheres.

**Results:** There were 5 males and 7 females with age ranges (35-78 years). Most of the strokes were in the MCA territory, with infarct size ranges (27.05-205.6 ml) and NIHSS (7-18) at baseline. The average ipsilesional FA values using ROIs in the genu and splenium were

0.74±0.05 and 0.82±0.07 at one month and 0.76±0.07 and 0.81±0.03 after 24 months of treatment, with no significant difference when compared to the corresponding contralesional region. The average ipsilesional MD (mm<sup>2</sup>/sec x 10<sup>-3</sup>) values of the genu and splenium were 0.85 ± 0.06 and 0.78±0.07 at 1 month and 0.85 ±0.06 and 0.79±0.07 after 24 months respectively, with no significant difference when compared to the contralesional regions. The ipsilesional FA in the splenium was lower and the MD was higher than in the contralesional hemisphere at all time points; however, none of the differences reached statistical significance. Dynamically both FA and MD of the contralesional splenium changed, whereas no pattern was recorded on the ipsilesional splenium. Tract based analysis of the genu and splenium recorded average FA values of 0.47± 0.04 and 0.57± 0.04 at one month and 0.48± 0.04 and 0.57± 0.04 at 24 months, respectively. There was no statistically significant difference between the FA values at one month and 24 months in both the genu and the splenium.

**Conclusion:** Longitudinal neuroimaging based quantification revealed no significant changes in white matter tract integrity or neuronal density in the genu and splenium regions of the corpus callosum; however, ipsilesional FA in the splenium was lower than contralesional FA at all time points, suggesting vulnerability of specific tracts.

# ABSTRACT

## Vigabatrin and Tuberous Sclerosis Complex

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Sponsored by: Hope Northrup, MD, Kit-Sing Au, PhD, Pediatrics

Supported by: National Institute of Neurological Disorders and Stroke, T35 NS 064931-05

Key Words: Tuberous Sclerosis Complex, Vigabatrin, 4-aminobutyrate aminotransferase

Tuberous sclerosis complex (TSC) is autosomal dominant disorder that is characterized by hamartomas. It has been found that up to 90% of TSC patients are affected by epilepsy. Many TSC patients have a specific type of epilepsy known as infantile spasms that are especially debilitating. In addition, TSC patients are at a higher risk for drug-resistant epilepsy than the general population. However, there is one drug, Vigabatrin, which is especially effective for TSC patients. Vigabatrin works to increase levels of gamma aminobutyric acid (GABA) in the brain by irreversibly inhibiting on the product of the 4-aminobutyrate aminotransferase (ABAT) gene, which catabolizes GABA. Although Vigabatrin's mechanistic pathway is known, the reasoning behind the Vigabatrin's increased efficacy in TSC patients is not. As Vigabatrin acts directly on the product of the ABAT gene, I sequenced this gene to look for sequence variations that could explain this correlation.

In this study, I focused on patients affected with TSC who had sporadic inheritance and a known gene mutation in either TSC1 or TSC2. I designed primers and performed PCR to amplify the specific ABAT exons from the DNA of these patients. In particular, I concentrated on exons 2, 3 and 15, as these are known to have gene mutations associated with neuropsychiatric symptoms. The amplified product was purified and sequenced using the BigDyeTerminator Sanger method. Sequencing products were fractionated and analyzed via the ABI 3130xl Genetic Analyzer. These results were examined looking for both previously identified polymorphisms for genotype phenotype association study and new variations.

I identified three new variants of ABAT that have not been described before. For the six ABAT polymorphic variants, I used contingency tables to compare allele frequencies between different subpopulations, such as TSC patients with and without seizures, to test for genotype phenotype association. In addition, these frequencies were analyzed against known European American population allele frequencies. I did find some correlation between TSC phenotypes and ABAT mutations, such as seizures and SNP rs1640998.

Although Vigabatrin has a high efficacy level in TSC patients, it is also associated with severe side effects such as permanent bilateral concentric visual field constriction in a small percentage of patients. If the unique relationship between Vigabatrin, and thus the ABAT gene, and TSC patients is known, patients that do not contain the genetic mutation associated with increased treatment efficacy will not be subjected to unnecessary risks.

## ABSTRACT

### Impact of Damage Control Laparotomy on the Timing of and Pulmonary Complications Associated with Femur Fracture Fixation

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Sponsored by: John A. Harvin, MD, Department of Surgery

Supported by: Center for Translational Injury Research (CeTIR)

Key Words: Femur fracture, damage control laparotomy

**Background:** Damage control laparotomy (DCL) has been shown to improve mortality in severely injured trauma patients in order to prevent or reverse the lethal triad of coagulopathy, hypothermia, and acidosis. Overzealous use of DCL and new concepts of resuscitation have led to an increase in the inappropriate triage to damage control. While certainly a vital tool, DCL is not without complication – it is associated with increased fluid losses, nutritional demands, rates of enteric fistula and incisional hernia, lengths of stay, and hospital charges. Numerous studies have shown that decreasing the time to femur fracture fixation leads to decreased pulmonary complication like acute respiratory distress syndrome (ARDS), pulmonary embolism (PE), and pneumonias (PNA). In patients undergoing DCL, femur fracture fixation may be delayed as the patient is considered “too sick.” We hypothesize that patients undergoing DCL will have increased time to femur fracture fixation and increased pulmonary complications.

**Methods:** Following IRB approval, the trauma registry was queried for all patients who presented to MHH-TMC from 1/1/09 to 3/1/14 who were  $\geq 16$  years, underwent emergent laparotomy, and had a femur fracture. Patients were then divided into those who underwent definitive laparotomy (DEF) and DCL. In addition, patients undergoing inappropriate DCL (pH  $\geq 7.25$ , temperature  $\geq 95^{\circ}\text{F}$ , and INR  $\leq 1.5$ ) were compared to the DEF group. Univariate analysis and purposeful regression modeling was used to analyze the outcomes of interest: pulmonary complications (ARDS, PE, PNA, respiratory failure) and time to femur fracture fixation.

**Results:** 106 patients met study criteria – 65 in the DCL group and 41 in the DEF group. No differences in demographics were seen. As expected, the DCL group was more severely injured (median ISS 34, IQR 27 and 43 vs 26, IQR 22 and 29,  $p < 0.001$ ) and more physiologically deranged (median ED base excess -8, IQR -12 and -5 vs -4, IQR -6 and -2,  $p < 0.001$ ). Postoperatively, the two groups were more similar except that postoperative SBP, platelet count, and PTT were statistically but not clinically different. For all patients, there was no difference in time to initial femur fracture fixation, but an increased time to internal femur fixation in the DCL group (median 71 hours, IQR 33 and 121 vs 32 hours, IQR 20 and 86). On purposeful logistic regression modeling, DCL was associated with an increased risk of pulmonary complications (OR 0.1, 95% CI 0.013-0.897,  $p = 0.039$ ). Patients who underwent inappropriate DCL (n 20) had a significantly longer time to initial femur fixation (median 35 hours, IQR 10 and 86 vs 17 hours, IQR 8 and 29).

**Conclusion:** Inappropriate triage to DCL is associated with an increased time to initial femur fracture fixation. DCL is associated with an increased time to internal femur fracture fixation. After adjusting for anatomic and physiologic markers of injury severity, DCL in patients with a femur fracture is associated with an increased risk of pulmonary complications. In these patients, the use of DCL should be reserved for only the most severely injured patients as liberal use may increase the rate of pulmonary complications.



## ABSTRACT

### Protocol Changes Effects on Nanopores after Electroporation

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Sponsored by: Derek West, MD, Department of Diagnostic and Interventional Imaging  
Supported by: Radiological Society of North America and The Department of Diagnostic and Interventional Imaging at The University of Texas Health Science Center at Houston  
Medical Student Research Award - RMS1427  
Key Words: Electroporation, Nanopores, Gold-Nanoparticles, PANC-1

**Introduction:** Electroporation uses voltage to create pores in biological cell membranes. Certain parameters are used to create pores reversibly, in order to deliver substances such as nucleic acids, proteins, nanoparticles, other compounds and combinations of them into cells, without killing the cells in the process. The best parameters for different conditions, cells, and substances have yet to be established. Protocol changes during different electroporation experiments vary the parameters used, such as: voltage (field strength), pulse length, number of pulses, pulse frequency, and duration of overall electroporation. We study the protocol changes in order to establish the most favorable conditions for pore size, duration of open pores, and maximum uptake with the use of differing size gold-nanoparticles conjugated with fluorescent tags for qualitative and quantitative analysis. A well-established research model of pancreatic adenocarcinoma cell line (PANC-1) was used, because electroporation and hopefully, in the future, drug delivery, was perceived as a promising and urgently needed alternative treatment option for this disease.

**Methods:** PANC-1 cells were cultured and then 0.5 million cells/well in suspension were electroporated in 25-well plates with one pulse of voltages 300V, 600V, 900V, and 1200V differing between wells, and a pulse length of 0.2ms. Each sample contained 0.01% Wt gold-nanoparticles conjugated with CY-5 (Au-NP-Cy5). The Au-NP-Cy5s differed in size between 30nm, 60nm, 90nm, and 125nm between individual wells. 5 replicates per sample were used. After electroporation, recovery, and prep, cells were taken to flow cytometry (FC) for quantitative analysis. Cells were also cultured in small petri dishes and electroporated with the same parameters. Afterwards, the adherent cell samples were prepped and fixed for light microscopy (LM) for qualitative analysis. Controls for both experiments consisted of plain cells and samples with each nanoparticle size all without electroporation.

**Results:** FC showed an average of 75% viability in most samples. There was a small detectable difference in the median fluorescence in most of the 60nm samples, but also others. LM showed slight fluorescence in all samples.

**Conclusions:** The results are inconclusive at the moment. The literature suggests that pores should only allow particles below 90nms to enter cells. Irreversible electroporation (cell death) should occur above 600-900Vs. For future directions, we plan to adjust techniques and use nanoparticles with tags that are easily detectable by the available FC lasers. We will run multiple experiments with different electroporation parameters changing one variable at a time.

Hopefully, once we find the best parameters for nanoparticle delivery, we can move on to use this knowledge *in vivo* to treat tumors grafted into mice and eventually to treat people.

# ABSTRACT

## Perioperative Variance Report Cards

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Sponsored by: Kuojen Tsao, MD, Department of Pediatric Surgery

Supported by: Kuojen Tsao, MD, Department of Pediatric Surgery

Key Words: patient safety, perioperative care, quality of care

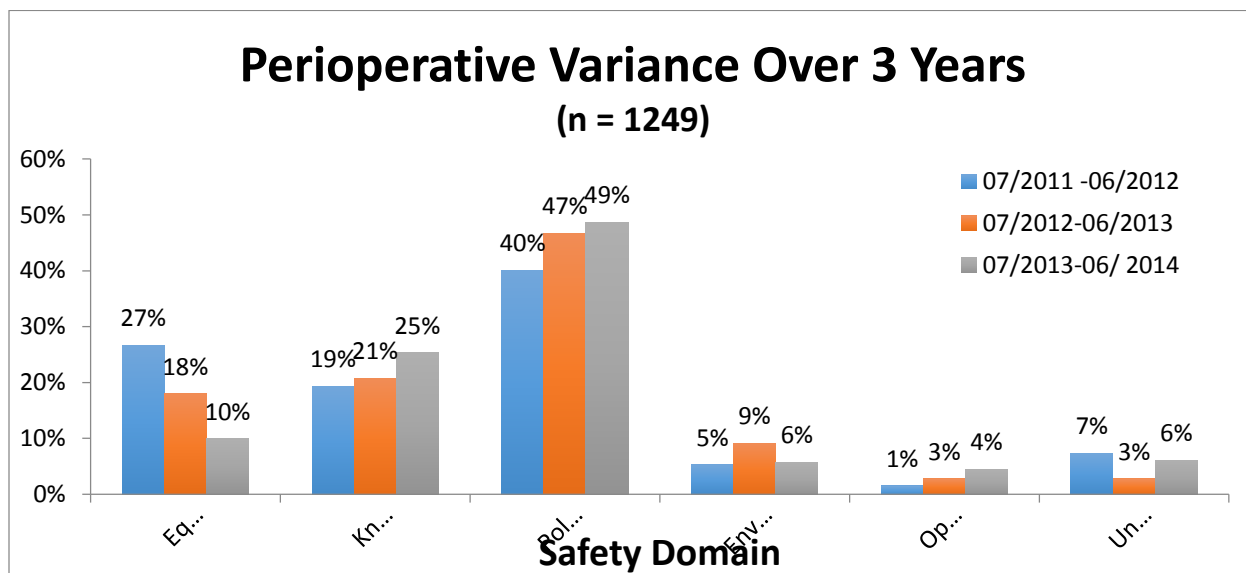
**Background:** To improve safety in the surgical wards, hospitals have traditionally relied on self-reporting of adverse events or variances via electronic reporting systems. However, these systems present a variety of challenges in real-world application, not the least of which are practical usability and distrust of provided anonymity. The result of these challenges is a dearth of provided responses highlighting safety issues. To counter this, a real-time system centered on report cards was implemented in the pediatric perioperative area. The purpose of this study is to quantify the adverse events reported through this system and to determine which areas have the most reported adverse events.

**Methods:** A “near miss/good catch” report card system that would allow users to describe in detail events compromising safety, outside the scope of normal patient care, was implemented. Every member of the surgical team was allowed anonymous access to these cards. Blank cards were placed in every pediatric operating room and in HIPAA-compliant lock-boxes at four perioperative locations. A subcommittee made up of anesthesiologists, surgeons, hospital safety officers, and other perioperative personnel collected the report cards weekly and grouped them into six safety domains (table), after which, the variances were taken up by the pediatric perioperative safety council for further action.

**Results:** 1,249 report cards were submitted over a 3 year collection period. 342 cards were collected in the first year, 362 cards were collected in the second year, and 545 cards in the third year. The collection box in the operating room common area received 80% of report cards, post-anesthesia care unit 9%, pre-operative area 7%, and waiting room 4%. Consistently across 3 years period, the most commonly reported variances involved policy/process (figure). The variances included adverse events (1%), near misses/good catches (7%) and other patient care issues (92%).

**Conclusion:** The use of a weekly-monitored report card system in the pediatric perioperative area has allowed for the reporting of key safety issues, which might have otherwise gone unnoticed. The quantity of events reported has held at a steady level for the past three years, which highlights its sustainability and the level of comfort that perioperative personnel have with using this system. In addition, this system has directly led to the formation of subcommittees focused on the implementation of safety interventions based on reported adverse events. Ongoing research is necessary to determine the continued sustainability of the report card system, and comparison with the previously used electronic system is needed to determine the true benefits and efficiency of the one currently in use.

Safety Domain	Variance Includes
Equipment/Supplies	Equipment or supply unavailable for use when needed because dirty, broken or missing
Knowledge/Attitude	An unsafe lack of knowledge or unprofessional behavior
Policies/Process	A failed or missing policy or process that does not fit in other categories
Environment	Inadequate housekeeping or unsafe room environment
Operations	Inadequate staffing, leadership or supervision
Unable to categorize	Illegible or not enough information provided



## **ABSTRACT**

### **A Comparison of the King Vision Channeled, King Vision Non-Channeled, and Cobalt GlideScope Video Intubation Systems in Difficult Intubation Patients**

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Sponsored by: Carin A. Hagberg, MD, Department of Anesthesiology

Supported by: Carin A. Hagberg, MD, Department of Anesthesiology

Key Words: King Vision video laryngoscope, channeled blade, difficult intubations

**Introduction:** Endotracheal intubation is essential for maintaining an open airway in patients who are often times unable to self-ventilate, therefore the timing and accuracy of an intubation is essential. Direct laryngoscopy has been the standard technique of patient endotracheal intubations since the beginning. For years innovators have tried to invent new and improved blades of laryngoscopes that would help medical practitioners visualize the laryngeal structures better, and thus help successfully intubate normal and difficult intubation patients. Within the past few years, video laryngoscopes have been introduced as a new device that could possibly improve the visualization of the patient's laryngeal structures more effectively. Video laryngoscopes allow the intubator to not only view the patient's airway superiorly, but they also improve intubation safety and success by allowing the practitioner to visually monitor the process of the intubation, while he or she coordinates his or her movements. The full view of the epiglottis and vocal cords shown on the video laryngoscope improves the intubator's view of the patient's airway. The channeled portion of a laryngoscope is designed to aid in a quicker and more accurate placement of the endotracheal tube into the trachea for proper ventilation. It is hypothesized that the King Vision Video Laryngoscope with the channeled blade is more effective when used to successfully intubate patients who are difficult to intubate as compared to the Cobalt GlideScope. It is also hypothesized that the King Vision Video Laryngoscope with the standard blade is just as efficient as the Cobalt GlideScope.

**Methods:** 225 adult patients (> 18 years old) who are scheduled for an elective surgery requiring general anesthesia at either Lyndon B. Johnson General Hospital or Memorial Hermann Hospital (Texas Medical Center) will be split into 3 groups: 75 people randomized to Cobalt GlideScope, 75 randomized to the King Vision Video Laryngoscope with the channeled blade, and 75 randomized to the King Vision Video Laryngoscope with the standard blade. A conventional endotracheal tube will be used. Subjects are selected based on meeting at least 2 of the following criteria: Mallampati III-IV, neck circumference > 43 cm, thyromental distance < 6 cm, or a mouth opening < 4 cm. After anesthesia is administered and ventilation of the patient begins, a resident of anesthesiology will perform the intubation. The results of the number of attempts and the intubation time will be recorded. The resident will have up to 2 attempts to successfully intubate a patient with their assigned laryngoscope. After 2 unsuccessful attempts

of intubation, the attending anesthesiologist will attempt the intubation with the same laryngoscope. If the attempt is still unsuccessful, then the attending may use the laryngoscope of his or her choosing and the case is recorded as a failure.

**Results:** as of 8/1/2014 data collection is ongoing, therefore results are unavailable at this time.

## ABSTRACT

### Morphological Defects of Retinal Tissue in Mouse Models with Circadian Clock Pathway Knockouts

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Sponsored by: Christophe Ribelayga, PhD, Department of Ophthalmology

Supported by: NIH grant EY018640 to CR

Key Words: sensory system, anatomy, retina, circadian rhythms, clock genes

**Background:** Circadian clocks are cellular time-keeping mechanisms that rely on a set of so-called “clock genes” and “clock proteins” interlocked in transcriptional/translational feedback loops. The key element of the positive loop is the Brain and Muscle ARNT-like protein-1 (BMAL1) and Circadian Clock Kaput (CLOCK) transcription factor heterodimer. At the beginning of a cycle, BMAL1:CLOCK enhances the expression of many clock-controlled genes, including the clock genes *Period (Per)* and *Cryptochrome (Cry)*. Newly synthesized PER and CRY proteins enter the nucleus ~ 12 hours later and repress BMAL1:CLOCK activity. The out-of-phase rhythms of transcription and translation of the clock genes together with the kinetics of degradation of the clock proteins generate circadian rhythms in gene expression with a period close to 24 hours. Mutations disrupting clock function in mice impacts retina gene expression and function. Here we determined whether the gross retinal morphology was affected by circadian clock dysfunction in various mouse models with circadian clock pathway knockouts.

**Methods:** Mice of the following genotypes: *Bmal1<sup>-/-</sup>*, *Cry1<sup>-/-</sup>;Cry2<sup>-/-</sup>*, *Cry1<sup>-/-</sup>;Cry2<sup>+/+</sup>*, *Per1<sup>-/-</sup>;Per2<sup>-/-</sup>*; and wild type C57/B6 were euthanized by cervical dislocation. The eyes were promptly harvested, fixed in paraformaldehyde, cryoprotected and cryostat sectioned into 12 μm slices. Sections were then stained with either DAPI or toluidine blue to stain DNA and acidic tissue components, respectively to be observed with fluorescent or normal light microscopy.

**Results:** Marked differences were found between genotypes in retinal layer thickness, the number of cells per layer, and the gross morphology of retinal tissue. All mutant genotypes exhibited thickening of the neural retina, particularly of the inner plexiform layer. *Bmal1<sup>-/-</sup>* and *Cry1<sup>-/-</sup>;Cry2<sup>-/-</sup>* indicated a ~10% reduction in cell numbers across all retinal layers. In contrast, *Per1<sup>-/-</sup>;Per2<sup>-/-</sup>* and *Cry1<sup>-/-</sup>;Cry2<sup>+/+</sup>* showed a ~10% increase in retinal thickness and cell number. Distinct gross morphological defects were observed in *Bmal1* mutants, including a typical wave-like organization of the outer nuclear layer along with a thickened inner plexiform layer.

**Conclusion:** The results clearly indicate that disruption of clock function leads to disorganization of retinal structure. The decreased cell count in *Bmal1<sup>-/-</sup>* retinas may reflect diminished activity from the positive limb of the clockwork. Conversely, the increased cell number observed in *Cry* and *Per* mutants may reflect constitutive activation of the positive limb in the absence of a negative loop. Moreover, the thicker plexiform layer in *Bmal1<sup>-/-</sup>* retinas where synapses occur may underline their functional impairment. This study demonstrates that in addition to being required for normal retinal function, proper circadian clock function is critical for normal lamination and anatomical organization of retinal tissue.

## ABSTRACT

### A Comparison of Healing Rates between Racial Groups in Patients with Venous Stasis Ulcers in Diabetic and Non-diabetic Patients from the Largest Wound Care Clinic Database in the United States

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Sponsored by: Adelaide A. Hebert, MD, Department of Dermatology

Supported by: National Institute of Diabetes and Digestive and Kidney Disease,  
2T35DK007676-21A1

Key Words: Venous Stasis Ulcer, Venous Insufficiency

**Background:** Venous stasis ulcers (VSU) affect approximately 1% of the adult population in the United States and represent the most common form of chronic lower extremity wound. VSUs are thought to occur as an end result of chronic venous insufficiency. In the setting of valvular incompetence and chronic venous insufficiency, blood pools into and stretches the veins of the lower extremities. This process results in the leakage of inflammatory cytokines and subsequent deposition of fibrinogen and collagen along the vessels and particularly the capillaries of the lower extremity. When the burden to the surrounding connective tissue becomes too high, the overlying cutaneous tissues become inadequately perfused, ischemic, and predisposed to necrosis. These connective tissues are thus biologically altered in a manner that prevents normal wound healing.

Diabetic patients tend to have multiple comorbidities such as renal failure, obesity, and vascular disease that affect wound healing. Certain patient groups, such as African Americans and Hispanics, have higher rates of each of these comorbidities. Thus, a comparison of VSU healing rates amongst racial groups becomes of value. The purpose of this study is to discern if lower extremity ulcers in diabetic patients have different patterns of healing when compared to non-diabetics.

**Methods:** Using de-identified patient data gathered from the U.S. Wound Registry, the VSUs of 30,954 Caucasian (N=25,776), African-American (N=3,159), and Hispanic (N=2,019) patients and 33,948 diabetic (N=15,030) and non-diabetic (N=18,918) patients were analyzed by Strategic Solutions Inc. Key comparisons were made regarding VSU size, healing rates after one year of treatment, and prevalence of diabetes among racial groups. Descriptive statistics were obtained using PASW 19 (IBM, Chicago): mean (standard deviation) for normal variables, median/interquartile range for non-normal variables, and percentages for categorical variables.

<b>Results:</b>	Median VSU Size (cm <sup>2</sup> )	Ulcer Healed: 1 year (%)	Diabetes Prevalence (%)
Caucasian	2.08	51.6	36.1
African-American	2.88	51.9	41.8
Hispanic	1.87	51.2	42.5
Diabetic	2.20	54.6	100
Non-Diabetic	2.09	48.9	0

**Discussion:** All studied racial groups, regardless of differing prevalence of diabetes and median VSU sizes had similar healing rates at one year of treatment. Surprisingly, in this database, diabetic patients had higher healing rates than non-diabetic patients despite having a larger median ulcer size. Hispanic patients had the highest prevalence of diabetes yet the smallest median ulcer size. African-American patients had a substantially larger median ulcer size (38.4% larger than the ulcers of Caucasian patients and 54% larger than the ulcers of Hispanic patients). Many factors may play into these results. First, socioeconomic factors can limit access to medical treatment. Second, cultural standards may alter how early patients seek medical treatment. Third, diabetic patients are more likely to have frequent routine checkups compared to non-diabetic patients. Fourth, age is a large determinant in effective healing, development of chronic venous insufficiency, and subsequent development of VSUs. This can offer insight regarding the increase in ulcer healing rates witnessed in diabetics.

**Conclusion:** Healing rates across races at one year were relatively equal for VSUs of the lower extremities. Unexpectedly, healing rates for diabetic patients were higher than those of non-diabetic patients. As VSUs constitute a billion dollar per year expenditure within the healthcare budget, understanding aspects of ethnicity, wound duration, and therapeutic intervention are essential to improving outcomes. This retrospective analysis constitutes an introductory effort to better understand the parameters that most impact outcomes for VSUs of the lower extremities.



## ABSTRACT

### Ileus: Molecular Pathway in GI Hypomotility

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Supported by: National Institute of Diabetes and Digestive and Kidney Disease,  
2T35DK007676-21A1

Key Words: Ileus, PAK, cytokines

**Background and Significance:** Ileus, defined as hypomotility of the gastrointestinal tract, is a widespread, clinically significant problem in trauma and critically ill patients. Ileus prevents enteral feeding, lengthens hospital stays, and increases patient complications and morbidity, impacting patient care costs significantly. The pathological basis of ileus is a complex mechanism involving inflammation, intestinal edema development, and smooth muscle dysfunction.

**Hypothesis:** The hypothesis is that surgical trauma-induced inflammation causing increased production of inflammatory cytokines/chemokines, up-regulates PAK1 activity and subsequently inhibits myosin light chain phosphorylation leading to intestinal smooth muscle paralysis.

**Experimental Design:** Experimentation will be conducted on primary human intestinal smooth muscle cells (hISMCs). Human ISMCs will be pre-treated with cytokines then subjected to either control cyclical stretch (CCS), simulating normal conditions, or edema cyclical stretch (ECS), simulating stress that cells undergo during post-surgical edema development. Significant edema development occurs after gut manipulation. This method will be used to define the potential role PAK1 plays in cytokine induced down-regulation of MLC phosphorylation

**Measurement:** PAK1 phosphorylation, MLC phosphorylation and protein levels will be measured by western blotting. PAK activity will be measured using an ELISA format with a primary antibody specific for the phosphorylated substrate of PAK.

**Results/Data:** As of 07-25-2014, data collection is ongoing and results are forthcoming.

## ABSTRACT

### Comparison of Screening Tools' Ability to Detect Sepsis Accurately

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Sponsored by: Laura J. Moore, MD, Department of Surgery

Supported by: Center for Translational Injury Research (CeTIR)

Key Words: Sepsis, Diagnostic Tools

**Background:** Sepsis, defined as whole-body inflammation stemming from a severe infection, is the primary cause of perioperative mortality and the leading cause of death in non-cardiac intensive care units. In order to reduce the mortality stemming from this condition, it is crucial that healthcare workers recognize and treat sepsis early. To address this issue, Dr. Laura Moore constructed and evaluated a sepsis screening tool that utilizes concise parameters of SIRS. Dr. Moore's screening tool quantifies the parameters into an overall numerical value, providing a means to triage those identified with sepsis and allowing for a high degree of selectivity and specificity. The Modified SIRS Criteria Screening Tool has been previously utilized in the Methodist Hospital SICU, leading to a decrease in sepsis-related mortality by one third. However, Memorial Hermann Hospital (MHH) currently utilizes the St. John Sepsis Alert (SJSA), an automated screening tool embedded in the EMR, to screen for septic patients. Although SJSA is utilized in many hospitals throughout the country, its performance characteristics have not been evaluated in any patient population. The purpose of this study was to compare Dr. Moore's screening tool with the SJSA.

**Methods:** Dr. Moore's screening tool was compared with the SJSA in the same patient population at Memorial Hermann Hospital (MHH). Epidemiologic and compliance data related to sepsis was collected prospectively from the EMR by employing data feeds through the Health Level 7 protocol (HL7), which allowed for data to be obtained pertaining to electronic charting tools, vital signs monitors, and hospital lab equipment. A total of 276 patients from the SIMU were included in the study, and 47 of these patients were septic.

**Results:** The St. John's Sepsis Alert was determined to have a sensitivity of 46.8%, a specificity of 84.3%, a PPV of 37.9%, and an NPV of 88.5%. In comparison, the Modified SIRS Criteria Screening Tool was found to have a sensitivity of 72.3%, a specificity of 88.2%, a PPV of 55.7%, and an NPV of 94.0%.

**Conclusion:** Despite the fact that SJSA had constant surveillance over patients' EMRs, it still detected less septic patients than the Modified SIRS Criteria Screening Tool which was performed twice a day. The difference in sensitivities and NPVs between the two tests is of particular importance, as this indicates that the SJSA is more prone to missing sepsis diagnoses. This study establishes a basis for the utilization of the PI's screening tool instead of the SJSA.

## **ABSTRACT**

### **Improving End of Life Discussions in Families of Patients with Severe Stroke**

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*Class of 2017*

Sponsored by: Nicole R. Gonzales, MD, Department of Neurology

Supported by: National Institute of Neurological Disorders and Stroke, T35 NS 064931-05

Key Words: stroke, end-of-life discussions (EOL)

**Background:** Catastrophic strokes occur unexpectedly, leaving patients incapacitated. This limits the decision making ability of the patient and therefore families must decide to remove life sustaining treatment or continue aggressive life supporting care. The task of informing patients' families falls to the entire health care team, but most especially to physicians. Currently, there is not a standardized process for delivering bad news at Memorial Hermann Hospital-Texas Medical Center. The purpose of this project is to define our current process, measure performance, and then organize the delivery of bad news into a formal structure.

**Methods:** From our stroke registry we identified patients during a three year period with severe stroke, defined as discharge to hospice or modified rankin scale (mRS) score of  $\geq 5$ . A chart review of these patients recorded the following: dates and times of decision about the plan of care relative to admission, DNR status and time/date this decision was made, comfort measures/hospice care, documented discussion of prognosis with families and which teams were involved, length of stay, demographics and clinical characteristics. Additionally we observed current procedures for delivering bad news. A study team member accompanied stroke neurologists during EOL discussions with patient families and evaluated their performance based on the following criteria: attitude of news giver, clarity of message, privacy, ability to answer questions, sympathy, time for questions, location of conversation, timing of conversation, and rank/seniority of the discussion leader.

**Results:** From observation of current EOL discussions we determined that important factors such as the availability of clergy, location of conversation, timing of conversation, and rank/seniority of discussion leader were variable and influenced the overall quality of the discussion. Chart review is ongoing and analysis will be forthcoming.

**Conclusion:** Our current system has the right personnel, knowledge and experience to inform family members but lacks a formal protocol for delivering bad news. We can use the information from this study to develop an educational intervention for health care teams which will lead to improved delivery of bad news.

## ABSTRACT

### Efficacy of Thromboelastography in Predicting Risk of Pulmonary Embolism in Orthopaedic Trauma Patients

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Sponsored by: Joshua L. Gary, MD, Department of Orthopaedic Surgery, Andrew R. Burgess, MD, Department of Orthopaedic Surgery

Supported by: Center for Translational Injury Research (CeTIR)

Key Words: Thromboelastography, pulmonary embolism, orthopaedic trauma

**Background:** Pulmonary embolism (PE) can be a deadly outcome for trauma patients despite aggressive surveillance and prophylaxis. Thromboelastography (TEG) has recently come into focus as a method for screening injured patients for hypercoagulability and risk for pulmonary embolism. The maximal amplitude (mA) value, representative of clot strength, is currently used to assess patient risk of PE in our trauma center. The purpose of this study is to determine whether the location of injury (upper extremity, lower extremity/pelvic, or spinal column) affects the risk of PE in orthopaedic trauma patients. It is hypothesized that patients with an isolated lower extremity/pelvic fracture will have higher mA values, predicting a higher risk for PE.

**Study Design:** The study included all patients admitted with admission TEG between January 1, 2011 and July 1, 2014 at a large level I trauma center. Subjects included patients ages 16 and older suffering a fracture from proximal humerus to distal radius (upper extremity), from pelvis to talus (lower extremity), or along the spinal column. Patients were excluded if their PE was diagnosed before arrival.

**Results:** 1927 musculoskeletal trauma patients were included in the study. 201 (10.4%) were diagnosed with PE. 1.4% of patients with an isolated upper extremity injury, 4.7% of patients with an isolated lower extremity injury, and 43.2% of patients with an isolated spinal column injury developed a PE. Also, 11.5% of the patients with injuries to more than one of these locations ("poly-trauma") developed a PE. An ANOVA with tukey post hoc analysis was used to compare the average mA values across these injury groups, accounting for race, gender, and age. The mean mA and p values are shown in the table below for the different groups compared.

**Discussion:** There was no significant difference in mean mA values across the stratified injury groups to indicate a difference in risk for PE. The elevated mA values seen in both PE and non-PE groups could be explained by the fact that all patients in the cohort underwent musculoskeletal injury, which could contribute to patient hypercoagulability. Further study should be performed to determine if specific fractures within these injury subsets have significantly different mA values and risk for PE. The relationship of mA values to timing of PE should be investigated.

<b>Injury</b>	<b>Solo Upper Extremity</b>	<b>Solo Lower Extremity</b>	<b>Solo Spinal</b>	<b>Poly- Trauma</b>	<b>All</b>
mA (non PE)	64.5	64.4	63.3	64.3	64.3
mA (PE)	66	62.6	61.9	65	63.8
P value	0.72	0.11	0.39	0.41	0.28

## ABSTRACT

### Poor Glycemic Control Associated with Lower Femur Neck BMD in Type 2 Diabetic Patients

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*Class of 2017*

Sponsored by: Nahid J. Rianon, MD, DrPH, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases  
2T35DK007676-21A1

Key Words: Type 2 Diabetes, FRAX, Bone Mineral Density, Osteoporosis

**Objective:** Patients with diabetes mellitus are at increased risk for osteoporotic fractures. The underlying mechanism of how diabetes affect bone metabolism is still unclear. Recent studies found that diabetic patients with poor glycemic control are associated with lowered serum osteocalcin level (a marker for bone turn over), which can lead to an increased risk of fracture. We aim to examine the association between HbA1C level in type 2 diabetic patients and their risk of fracture using two parameters: 1) 10-year probability of developing osteoporotic hip fracture as assessed using FRAX and 2) femur neck bone mineral density (BMD).

**Methods:** A cross-sectional questionnaire survey enrolled 79 patients (56% women and 44% men) 50 years or older who visited UT Physician Endocrinology clinic for type 2 diabetes mellitus management between June 13th, 2014 and July 30th, 2014. Electronic chart review collected information on latest HbA1C level and their BMD test result if available. A bivariate analysis described patient characteristics by high (>7) and low ( $\leq 7$ ) HbA1C. A multivariate regression analysis reported association between HbA1C and risk of fracture in terms of FRAX and BMD in women only (men excluded from regression analysis due to small N). The model was adjusted for age, height, weight and ethnic/racial background.

**Results:** Mean age ( $\pm$ SD) for all 79 patients was 66 ( $\pm 9$ ) years. There was no significant differences of age, height, weight, gender, ethnic and racial background, FRAX score between the high and low HbA1C groups. BMD report was available for 15 women and 1 man. The association between low femur neck BMD and high HbA1C remains significant in the multivariate regression analysis ( $\beta$  coefficient -3.59, 95% confidence interval -6.38 to -0.79) for women.

**Conclusions:** Poor glycemic control (higher HbA1C) in type 2 diabetic patients may increase fracture risk due to lower femur neck BMD compared to those with good glycemic control. FRAX was not a helpful tool to identify higher risk of fracture in our study patients.

## **ABSTRACT**

### **Opioid Antagonism Affects Attention to Emotional Stimuli**

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Sponsored by: Margaret Wardle, PhD, Department of Psychiatry and Behavioral Sciences

Supported by: The Bernard Saltzberg Summer Research Fellowship, and the National Institute on Drug Abuse grant R01 DA02812 to Dr. Harriet de Wit

Key Words: Opioid antagonism, attention, addiction

Naltrexone (NTX), an opioid antagonist, is used to treat alcohol and opioid addiction, but its clinical acceptance has been limited by high rates of noncompliance with medication use. The lack of compliance may be due in part to the effects of the opioid antagonist on other motivational and hedonic functions. The opioid system is implicated in hedonic (pleasurable) experiences, particularly pleasure resulting from positive social interaction. Opioid agonists increase social play in rats and primates by enhancing its rewarding effects. On the other hand, opioid antagonists reduce the hedonic effects of social interaction, while simultaneously increasing motivation to seek social interaction. NTX does not produce frank depression in humans, but these results in animals suggest it may subtly alter hedonic responses to social interactions. Here we administered NTX to healthy human volunteers to evaluate its effect on responses to facial expressions, which are critical social interaction cues, at two early stages of social behavior, initial attentional capture and attentional engagement. We hypothesized that NTX would increase first-look attention capture by positive emotional faces, consistent with increased motivation to seek positive social stimuli, but would decrease prolonged attentional engagement by positive emotional faces, consistent with attenuated responses to positive social stimuli.

Over three sessions, 26 healthy volunteers received NTX 25 mg, 50 mg, and placebo under counterbalanced double-blind conditions. During expected peak drug effect, participants completed a task consisting of a series of 2-second trials during which a pair of faces, one a neutral expression and one an emotion (happy, sad, angry, fearful) posed by the same actor, were presented. During each trial, direction of initial fixation of gaze (attentional capture) and length of gaze (attentional engagement) to emotional vs. neutral stimuli were measured using electrooculography (EOG). The Profile of Mood States (POMS) measured typical subjective drug effects on elation and fatigue throughout the session. Data were analyzed using a planned comparison approach to within-subject ANOVA.

NTX increased self-reports of fatigue and decreased reports of elation, indicating that it produced its typical subjective effects. NTX increased first-look attentional capture by all emotional pictures compared to placebo, but did not differentially affect positive emotional pictures. NTX did not have an effect on length of gazes at emotional stimuli.

Contrary to our hypotheses, NTX did not cause participants to initially look at or gaze longer at positive expressions compared to negative expressions. However, NTX increased the

probability of first orienting to any emotional expression. This is broadly consistent with the idea NTX creates a “social deficit”, leading to solicitation of social stimuli and interaction, similar to findings in laboratory animals. These findings are relevant to opioid and alcohol addiction treatment because NTX may impact a patient’s ability to derive benefit from social relationships and support, an important factor in the successful treatment of addiction. Further study is needed to evaluate whether NTX produces similar changes in an addicted population, and whether these changes carry over into social behavior and interactions in daily life.



## ABSTRACT

### TSPO as an Indicator of Microglia Activation and Neuroinflammation in Traumatic Brain Injury

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Sponsored by: Charles S. Cox, Jr., MD, Department of Pediatric Surgery

Supported by: Charles S. Cox, Jr., MD, Department of Pediatric Surgery; The University of Texas Medical School at Houston – Office of the Dean

Key Words: Traumatic Brain Injury, Microglia, PTBR, TSPO

Traumatic brain injuries are characterized by an inflammatory response in the injured brain, resulting in the infiltration of leukocytes, activation of glial cells, microglia and astrocytes and ultimately, the release of pro- and anti-inflammatory cytokines. This neuroinflammation occurs rapidly and is believed to be the cause of a number of both beneficial and detrimental effects (Woodcock et. al. 2013). Microglia are resident macrophages that sense pathological tissue alterations and act primarily to protect and repair the brain when damaged. These cells have a low threshold of activation and will activate in response to even the most minor pathological changes in the CNS (Graeber 2010). Most TBI studies indicate that extended microglial activation becomes damaging over time, with autophagy possibly contributing to pathology through phagocytosis of healthy cells in addition to damaged tissues (Ramlackhansingh et. al. 2011; Hernandez-Ontiveros et. al. 2013). The Peripheral Type Benzodiazepine Receptor (PTBR), also known as translocator protein (TSPO) is localized on the outer mitochondrial membranes of reactive astrocytes, microglia and macrophages and its primary role is the transport of cholesterol across mitochondrial membranes (V. Papadopoulos, 1998). In patients with TBI, PET ligand binding to PTBR is significantly raised in various areas of the brain even after several months to years post injury (A. F. Ramlackhansingh et al.). Given that TBI results in prolonged inflammation and increased proliferation and activation of microglia we hypothesize that **TBI will result in a similar upregulation for PTBR and that PTBR/TSPO may serve as a viable marker to indicate inflammation in patients as well as in rodents.** A controlled cortical impact device (Leica.) was used to administer a unilateral brain injury in adult mice, and brains were harvested at either 24h, 72h or 28 days. Brains were then sliced with a Leica Vibratome into 30 micron slices and sections were stained using a standard free floating staining protocol (Bedi et al., 2013) with IBA1 and TSPO primary antibodies used for identifying microglia and PTBRs (respectively). Quantification of active/resting microglia was conducted by analyzing morphology of microglia in photomicrographs. Qualification of PTBR expression was conducted by visual identification of presence or absence of TSPO+ staining in the thalamus. Injured mice showed an increase in the total microglia/macrophage population at 72 hours ( $p < 0.05$ ) and 28 days ( $p < 0.001$ ) post-injury (but not at 24 hours), and a significant increase in activated microglia/macrophages bilaterally in the hippocampus at 72 hours and 28 days post-TBI. Qualitative assessments of photomicrographs indicated marked microglial/ macrophage

activation in the ipsilateral thalamus of the injured brains as well as marked increase in TSPO+ cells in the thalamus at 28 days in all injured slices (4/4). There was no TSPO+ staining present in the uninjured slices at 28 days (0/5). The data supports the notion that TBI and resulting prolonged inflammation are linked to an upregulation of the PTBR. Thus, changes in PTBR expression (monitored in vivo using PET ligand [11C](R)PK11195/PBR28) could potentially be used to monitor treatment progress over long periods of time, in correlation with changes in cognitive behavior.



# Undergraduate Students

## ABSTRACT

### Visualizing the Innate Immune Response to Tuberculosis

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Sponsored by: Jun Liu, PhD, Department of Pathology and Laboratory Medicine

Supported by: Jun Liu, PhD, Department of Pathology and Laboratory Medicine

Key Words: Tuberculosis, Visualization, Macrophage, Scanning Electron Microscopy

Tuberculosis (TB) is the most common infectious disease worldwide; its etiological agent *Mycobacterium tuberculosis* (*Mtb*) is present in more than a third of the global population. While much is known about the overall immune response, it is still unknown as to why granulomatous *Mtb* will cause necrotic tissue damage, develop into latency, or will heal to form a Ghon complex. Current efforts focus on whether these outcomes are determined by the initial innate immune response to *Mtb* infection. We aim to examine the trafficking within an infected macrophage host during the initial stages of infection by three-dimensional (3D) modeling of the *Mtb* bacteria within macrophage host cells during the innate immune response, using scanning electron microscopy (SEM). Such an approach has previously been impractical because of the noise-to-contrast ratios in other microscopy techniques at this scale. J774A.1 macrophages were exposed to either *Mtb* or non-virulent BCG ( $10^5$  CFU/mL; 4 or 24 hr, 37°, glass slide) and then prepared with an osmium tetroxide stain. A macrophage monolayer was then embedded in Epoxy resin (LX112). Scanning electron microscopy using Gatan 3View SEM took ~600 cross sections 50nm thick at an 8000x8000 resolution. Image processing, segmentation, and surface rendering was done via Amira 5.2.2 and Amira 5.6.0. In examining the reconstructed cellular model, we identified macrophages infected with mycobacteria; we also found an increase in vesicle formation in *Mtb* infected macrophages when compared to the non-virulent BCG pairs. These results highlight the usefulness of 3D models generated by this novel application of SEM. Future research will expand this model to quantify the number and the volumes of vesicles that appear post-infection as a measure of the cellular immune response induced by *Mtb*.

## **ABSTRACT**

### **Effects of Combined Sustained Hydrostatic Pressure and Laminar Shear Stress on the Licensing of Mesenchymal Stromal Cells (MSCs) to Express Anti-inflammatory Genes**

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Sponsored by: Pamela L. Wenzel, PhD, Department of Pediatric Surgery

Supported by: The State of Texas Emerging Technology Fund, The ASH Scholar Award, NIH 1K01DK092365-04

Key Words: Mesenchymal Stem/Stromal Cells, Hydrostatic Pressure, Laminar Shear Stress

Excessive inflammation can cause or exacerbate multiple types of diseases and injuries. Mesenchymal stromal cells (MSCs) can display immunoregulatory functions to combat this inflammation by releasing cytokines that signal macrophages and other immune cells to convert to anti-inflammatory phenotypes. To exert these effects, MSCs must first be activated, or licensed, by either direct or indirect interaction with inflammatory cells or cytokines. Biomechanical signals, such as laminar shear stress (LSS) and hydrostatic pressure, have recently been shown to be an effective method of licensing MSCs to display an anti-inflammatory phenotype as well. In this study, we developed a system to apply both sustained hydrostatic pressure and laminar shear stress to MSCs in order to determine whether combining these two forms of biomechanical stress elicits a stronger immunosuppressive response than either one alone. Gene expression data was collected for key immunoregulatory genes *COX2*, *TSG6*, *IL1RN*, and *HMOX1* after applying pressure and LSS for 30 min, 3 h, 8 h, and 24 h. The data from qRT PCR at these time points showed a gene expression trend similar to the ones observed in analogous experiments using both biomechanical stressors alone, suggested that combining the two stressors does not have a detrimental effect on the immunoregulatory effects of the MSCs. To determine the efficacy of using both stressors in place of just one, gene expression of MSCs subjected to LSS and pressure for 3 h was compared to gene expression of MSCs subjected to LSS alone and pressure alone, both for 3 h. Gene expression in the MSCs subjected to both stressors was significantly higher than that in the MSCs subjected to pressure alone, but was not conclusively higher than that observed in MSCs subjected to LSS alone. The combination of both hydrostatic pressure and LSS is clearly more effective in licensing MSCs than hydrostatic pressure alone, but future experiments are needed to determine whether it is more effective than LSS alone.

## ABSTRACT

### Expression of MMP-20 in Human Oral Squamous Cell Carcinoma

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Sponsored by: Kalu U.E. Ogbureke, BDS, MSc, DMSc, JD, FDSRCS, FDSRCPS, FRCPath  
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Supported by: UT-School of Dentistry at Houston, Research Office

Key Words: MMP-20, SIBLING Family of Proteins, Human Oral Squamous Cell Carcinoma,  
immunohistochemistry

**Background:** Among members of the matrix metalloproteinases (MMPs), MMP-20 (enamelysin) is unique in that its expression is regarded as tooth-specific. During tooth development MMP-20 is expressed prior to the onset of dentin mineralization, and has been shown to facilitate mineralization by cleaving a number of tooth matrix proteins, including dentin sialophosphoprotein (DSPP). Specifically, MMP-20 cleaves DSPP into dentin sialoprotein (DSP) and dentin phosphoprotein (DPP) during the maturation stages of tooth development. DSPP is a member of the *Small Integrin-Binding Ligand N-linked Glycoprotein (SIBLING)* family of extracellular matrix protein recently found to be upregulated in human oral squamous cell carcinoma (OSCC). The aim of this study was to explore the possibility of MMP-20 expression in human OSCC tissue by immunohistochemistry. This is with a view to further exploring any potential interaction of MMP-20 with DSPP in the biology of OSCCs.

**Methods:** Using immunohistochemistry techniques in a retrospective study on archived paraffin sections, 49 cases of human OSCC were screened for the expression of MMP-20. Negative control consisted of normal oral mucosa. Of the 40 cases selected, 14 were classified as “well-differentiated” (WD), 20 as “moderately-differentiated (MoD)”, and 15 as “poorly-differentiated” (PD) tumors. Immunoreactivity was scored as positive if > 10% of tumor cells stained for MMP-20, and negative if <10% of tumor cells failed to stain for MMP-20. Score were based on assessment of overall staining intensity and the number of positive tumor cells.

**Results:** Overall, 44 (~90%) of the cases showed immunoreactivity to MMP-20 with all (15) cases of PD, 19 (95%) of MoD, and 11 (79%) of WD tumors exhibiting positivity for MMP-20. Furthermore, immunoreactivity was largely cytoplasmic and perinuclear in distribution with punctate nuclear distribution, particularly in PD tumors.

**Conclusion:** MMP-20 is up-regulated in human OSCC. This result provides the basis for further investigation into the role of MMP-20 in the biology of oral cancers.

# ABSTRACT

## Cholesterol Metabolism in Craniofacial Development

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Supported by: UTHealth School of Dentistry Research Office and Junichi Iwata, DDS, PhD,  
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Key Words: Cholesterol metabolism, Craniofacial development, Cleft palate, Birth defects

**Introduction** Cleft palate is the most common congenital birth defect in the world. However, the etiology of cleft palate is largely unknown. Recent studies indicate that abnormal cholesterol diets and mutations in genes involved in cholesterol biosynthesis result in cleft palate, suggesting that cholesterol metabolic aberrations may be a widely conserved mechanism. However, it is still largely unknown how enzymes involved in cholesterol metabolism regulate craniofacial development.

**Objective:** The 7-dehydrocholesterol reductase (DHCR7) is an enzyme for cholesterol synthesis, and mutations in *DHCR7* lead to an overproduction of sterol intermediates and a reduction of mature cholesterol. In this study, we investigated the contribution of DHCR7 to craniofacial development.

**Methods** We performed gross phenotypic analysis and skeletal staining for newborn *Dhcr7* null (*Dhcr7*<sup>-/-</sup>) mice.

**Results** *Dhcr7*<sup>-/-</sup> mice died within one day after birth, with incomplete penetrance of cleft palate (approximately 9%) and reduced cholesterol amount. In addition, loss of *Dhcr7* resulted in a small mandible and impaired suture formation of the skull.

**Conclusion** Our findings indicate that loss of *Dhcr7* results in cleft palate and craniofacial skeletal defects. We will further investigate the molecular mechanism of cleft palate and skeletal defects in *Dhcr7*<sup>-/-</sup> mice. This study will lead to the innovation for the diagnosis, treatment and prevention of craniofacial birth defects.

## ABSTRACT

### Effects of *In Vivo* Application of Serotonin and Lipopolysaccharide on Tentacle Withdrawal Reflex of *Aplysia californica*

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Supported by: NSF IOS-1146987, *Comparisons of Functions and Mechanisms of Nociceptive Sensitization in Dissimilar Molluscs*; The University of Texas at Houston Medical School - Office of the Dean

Key Words: nociceptive sensitization, injury, memory, defensive behavior

*Aplysia* has been widely used as a model system to study mechanisms of learning and memory. *Aplysia* is also a good model for studying inflammatory sensitization mechanisms that may be related to pain. Serotonin (5-HT) is known to increase the excitability of nociceptive sensory neurons in *Aplysia* (and enhance synaptic transmission), but little is known about its behavioral effects when applied *in vivo*. In mammals, 5-HT is also an inflammatory mediator released that can sensitize primary nociceptors. Lipopolysaccharide (LPS) from gram negative bacterial cell walls potently triggers inflammatory responses in diverse species and releases 5-HT in mammals. This study tested the prediction that injection of 5-HT (250  $\mu$ l, 100  $\mu$ M) into a tentacle would produce ipsilateral sensitization of tentacle withdrawal, and to test whether LPS injection produces similar effects. Vehicle (seawater) injection into the contralateral tentacle was used as an internal control. The animal was tested twice before and then 5 min, 30 min, 1 hr, 2 hr and 18 hr post-injection. Test stimuli were 4 von Frey hairs of increasing stiffness applied to the tip and base of the tentacle. Responses were scored on a 5-point scale. 5-HT appeared to enhance ipsilateral tentacle withdrawal in each posttest, with statistically significant effects at 30 min and 2 hr. Additional experiments may reveal whether this ipsilateral sensitization also occurs at other times, and whether any general sensitization occurs. A single injection of LPS produced no evidence of sensitization or local inflammation. However, the open circulatory system of *Aplysia* rapidly distributes any injected agent, so the LPS may not have maintained a sufficiently high local concentration for a long enough period to have physiological effects. Longer-lasting, focal delivery of LPS will be necessary to fully test the possibility that LPS-induced inflammatory responses induce reflex hypersensitivity in *Aplysia*.



## ABSTRACT

### Comparison of RXR $\alpha$ -KO and Wild-Type Mice Following Stroke

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Supported by: NNINIH-NINDS-R01NS084292; The University of Texas at Houston Medical School - Office of the Dean

Key Words: Stroke, RXR $\alpha$ , MCA/CCAo

**Background:** Expression of two important nuclear receptors, retinoid X receptor alpha (RXR $\alpha$ ) and peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), which together function as a heterodimer, may represent an important step in transcriptional regulation of their target genes. Prior studies have established the beneficial role of PPAR $\gamma$  in neuroprotection and during recovery from stroke. We sought to determine whether RXR $\alpha$  also operates in this capacity, specifically with regards to the presence of cells surrounding the infarcted area involved in blood vessels and angiogenesis, microglia/macrophages (MM $\phi$ ), and axon regeneration.

**Methods:** Two-month-old male MM $\phi$  conditioned RXR $\alpha$ -knockout (KO) mice were compared to control littermates. Five animals were used per group. Each mouse received a stroke (60 minute left middle cerebral artery/common carotid artery occlusion - MCA/CCAo). Tissue was dissected for analysis 28 days following the stroke. After using the cryostat to cut 10  $\mu$ m coronal brain sections, the tissue underwent immunohistochemical staining to detect laminin (marker for vessel associated extracellular matrices), CD31 (marker for endothelium), neurofilament (marker for neurons), and CD68 (marker for MM $\phi$ ). The immunostains were then analyzed by quantitating a signal from fluorescent microscopy. Specifically, the intensity (per  $\mu$ m<sup>2</sup>) of the fluorescence in the peri-infarcted areas was measured. The difference between the two strains of mice was established using a two-sample two-tailed t-test with an alpha level of 0.05.

**Results:** The staining intensity for laminin, CD31, and CD68 was significantly greater (p-values of 0.0415, 0.0464, and 0.0494, respectively) in the peri-infarcted areas of RXR $\alpha$ -KO mice. There was no change (p-value of 0.7195) in intensity of staining from neurofilament.

**Conclusions:** Expression of laminin, CD31, and CD68 appears to be increased after stroke in the brains of KO mice, suggesting presence of augmented angiogenesis and inflammation in animals that lack RXR $\alpha$  in MM $\phi$ . RXR $\alpha$  has been proposed to have anti-inflammatory functions, suggesting reduced CD68 intensity could be a consequence of such anti-inflammatory activities. In addition, RXR $\alpha$  in MM $\phi$  plays an important role in supporting the effective phagocytosis-mediated brain cleanup after brain tissue death. Thus, it is possible that, at 28 days after stroke, the increased vascularization and number of MM $\phi$  can be explained by the ongoing cleanup.

On the other hand, less abundant vascularization and reduced presence of MM $\phi$  in control mice may signify the completion of the cleanup. Existing data also suggest that MM $\phi$  may release VEGF, a key factor for angiogenesis. Therefore, a more extensive vascular network in KO mice could also be due to the increased presence of MM $\phi$  in this brain region. Neurofilament, a structural component of axons, was not different between the two genotypes. We assume that RXR $\alpha$  at this delayed stage of stroke pathogenesis did not have an impact on neuronal abundance, and we cannot conclude that there is a difference between the two strains of mice.

## **ABSTRACT**

### **Voluntary and Reflexive Eye Movements in Parkinsonism**

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Supported by: Anne B. Sereno, PhD, Department of Neurobiology and Anatomy, NSF 0924636; Mya Schiess, MD; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Saccades, Parkinsonism, Parkinson's disease, Eye Movements

Parkinson's Disease (PD) and related disorders (Parkinsonisms, PS) are neurodegenerative disorders that over 60,000 Americans are diagnosed with each year. In the early stages, PD and PS have many overlapping symptoms, but their prognoses and ideal treatments are distinct. Therefore, a critical barrier to effective treatment is making an accurate diagnosis early in the disease course. Additionally, finding an objective measure to monitor disease progress that does not rely on the current subjective clinical tests would aid monitoring disease progression and evaluation of interventions. Small neurological changes affect eye movements before clinical symptoms present, so tracking various eye movements may serve as a sensitive and objective biomarker for early differentiation and monitoring of PD and PS.

To identify potential eye movement markers for disease differentiation, we measured the eye movements of PD (n=15), PS (n=15), and Control (n=13) subjects using an infrared eye tracker as they performed a prosaccade (reflexive) and antisaccade (voluntary) task. To identify markers for monitoring disease progression, a subset of the subjects (n = 13) were tested again 6 months after their first visit. The results show that both PD and PS patients had greater antisaccade error rates than controls ( $p < 0.05$ ). Critically, only PS patients exhibited slower prosaccade latencies than PD and Controls. Further, across a short time interval, only PS patients showed significant slowing of antisaccade latencies ( $p < 0.01$ ).

High antisaccade error rates in both PD and PS reflect frontal lobe impairment present in both diseases. In the prosaccade task, the impaired latencies of only the PS subjects suggest more widespread degeneration involving subcortical and brainstem regions. Hence, reflexive RTs may provide the most sensitive biomarker for early differentiation between PD and PS. Additionally, the significant slowing of antisaccade latencies in mid-late stage PS patients over short time intervals suggests that this variable may be a useful marker for tracking PS disease progression or efficacy of intervention.

## **ABSTRACT**

### **A New Neuronal Model for Studying Mechanisms of Nociceptive Plasticity in *Aplysia californica***

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Sponsored by: Edgar T. Walters, PhD, Department of Integrative Biology and Pharmacology

Supported by: NSF IOS-1146987, *Comparisons of Functions and Mechanisms of Nociceptive Sensitization in Dissimilar Molluscs*

Key Words: Sensitization, serotonin, activity-dependent synaptic facilitation

*Aplysia* has proven to be a useful model for studying memory and injury-related plasticity. We have developed a practical neural model in which the anterior tentacle nerve of *Aplysia* is used for test and conditioning stimulation while monitoring synaptic potentials from large, previously identified "Bn" motor neurons in the cerebral ganglion. This system can be used for efficient testing of injury-, pain-, and memory-related signaling and plasticity mechanisms. After gross dissection, I isolated the central nervous system in a 1:1 mixture of saline and isotonic MgCl<sub>2</sub> and desheathed the cerebral ganglion, allowing access to the B clusters containing the motor neurons. Two recording electrodes were inserted into a single Bn Cell; one to input hyperpolarizing current and the other to accurately record membrane potential. Three isolated pulse stimulators were used to acquire data; the first delivered a 500 ms hyperpolarizing pulse to test input resistance; the second a 1 s depolarizing pulse to test repetitive firing and excitability; the third to stimulate a nerve segment to look for evoked complex synaptic activity within the Bn neuron. To test the utility of this model I tested the effects of chemical stimulation of the ipsilateral tentacle nerve. To produce activity-dependent plasticity in the nerve and ganglion, I selectively depolarized a nerve segment with elevated K<sup>+</sup> solution for 2 minutes. The Bn neuron initially received intense excitatory input, and then displayed hyperexcitability and synaptic facilitation for at least 30 minutes after treatment. In another experiment I applied 100 μM serotonin (5-HT) (final concentration of 50 μM) to the nerve segment for 30 minutes. This produced little or no alteration of Bn responses. This new model should prove useful for undergraduates to gain productive research experience in neurophysiology.

## ABSTRACT

### Mesenchymal Stem Cells in Reducing TBI Chronic Inflammation

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Sponsored by: Scott D. Olson, PhD, Department of Pediatric Surgery

Supported by: Scott D. Olson, PhD, Department of Pediatric Surgery; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Traumatic brain injury, Mesenchymal stem cells, Bone marrow, Amniotic fluid

**Background:** Traumatic brain injury is one of the leading causes of death in the world, accounting for about 30% of all injury-related deaths. Even after trauma caused by primary injury, increased neuroinflammation can lead to secondary cell death and long-term brain deterioration. Unfortunately, there have been few, if any, treatments for the chronic secondary injuries following TBI. This provided reason to explore possible anti-inflammatory treatments, leading to the hypothesis that bone marrow (BM) derived and amniotic fluid (AF) derived mesenchymal stem cells, which have been shown to have anti-inflammatory effects could reduce secondary neurological damage.

**Methods and Results:** Therapeutic potential in vivo was tested in a rat model of severe TBI induced using a controlled cortical impact (CCI) device for both BM and AF MSCs. In separate groups of rats, 10,000,000 cells/kg of BM or AF MSCs from three different BM donors and 2 different AF donors were injected intravenously into the tail vein at 72 hours post-injury. In all groups, the rats were sacrificed 7 days after injury for immunohistochemical analysis of their brains. A *Leica VT1000 S* Microtome was used to cut 30  $\mu\text{m}$  mid-hippocampus slices expressing the injured areas, and staining for various inflammatory markers was performed. Using primary antibodies against IBA1, DCX, and GFAP, which are markers for microglia, doublecortin, and astrocytes, respectively, and secondary antibodies with *Alexa Fluor*<sup>®</sup> dye, stained slices were imaged, and analysis encompassed both counting stained cells and intensity measurements. Higher activated microglial counts correlate with increased pro-inflammatory cytokine secretion, and results showed that BM MSC's inhibition of microglial activity was more pronounced than that of AF MSCs. Additionally, increased astrocytic activity, which can lead to scarring, was found in AF MSC rats as opposed to a slight decrease in BM MSC rats compared to the CCI control. Conclusive data from doublecortin+ cells, indicators of neurogeneration, could not be drawn because of variable counts.

**Conclusion:** Bone marrow derived show promise in reducing inflammation associated with secondary TBI injuries and may be useful in future therapies. Additional research to understand the distinct mechanisms by which these treatments function may be future areas of focus. In parallel, further research involving anti-inflammatory drugs and intervention with combinations of treatments to reduce long-term consequences may improve well-being of TBI patients.

## ABSTRACT

### The Role of p53 in *Xenopus* Embryonic Kidney Development

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Sponsored by: Rachel K. Miller, PhD, Pediatrics

Supported by: Rachel K. Miller, PhD, Pediatrics

Key Words: Kidney, p53, differentiation

p53 is a well-studied tumor suppressor protein that has also been shown to play a role in embryonic kidney development. Studies utilizing p53 knockout mice and dominant negative mutant forms of p53 in *Xenopus laevis* (frog) embryos demonstrate that reduction of p53 activity leads to reduced cell differentiation within the nephrons (Saifudeen et al. *JCI*. 2002). This can lead to multiple kidney defects including tumorigenesis and cystogenesis (Wallingford et al. *Curr Biol*. 1997 and Saifudeen et al. *JCI*. 2002). In some patients with Li-Fraumeni syndrome, a human disease caused by mutations in p53, reduced nephron differentiation leads to a pediatric kidney cancer, Wilms tumor (Hartley et al. *Cancer Genet Cytogenet*. 1993). Chip-Seq and microarray experiments using embryonic mouse kidney suggest that p53 regulates the transcription of Wnt genes (Li Y et al. *Physiol Genomics*. 2013). Specifically, Wnt components that are part of the  $\beta$ -catenin destruction complex are upregulated by p53 (Li et al. *Physiol Genomics*. 2013). Based on work from other groups, we hypothesize that p53 regulates Wnt signaling during embryonic kidney development, leading to the downregulation of  $\beta$ -catenin. To test our hypothesis, our initial objectives were to assess the expression of p53, to confirm its knockdown in embryos and to observe the phenotype upon its knockdown within *X. laevis* kidney. p53 protein expression was highest from embryonic stages 9-18, overlapping with kidney development. Knockdown of p53 using stabilized antisense oligonucleotides (morpholinos) was assessed via Western blot. Immunofluorescence was used to observe the phenotype from p53 knockdown within the embryonic kidney. While the knockdown of p53 was not detected by Western blot, a phenotype was observed within the kidney. Markers of the differentiated kidney were highly reduced upon p53 knockdown as compared with control conditions. Overall, our work has demonstrated that p53 is expressed during embryonic kidney development and that the knockdown of p53 within the kidney results in reduced differentiation of nephron structures.

## ABSTRACT

### Reconstitution of a Gram Positive Pilus Assembly Machine *in vitro*

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Class of 2014

Sponsored by: Hung Ton-That, PhD, Department of Microbiology and Molecular Genetics

Supported by: NIH grant R56AI061381 – Ton-That (PI)

Key Words: Gram-positive bacteria, pili, pilin-specific sortase, transpeptidase

Pili are bacterial virulence factors. In Gram-positive bacteria, pili are assembled and covalently anchored to the cell wall by cysteine-transpeptidase enzymes known as sortases. A well-studied pilus system is the Spa-type pilus of *Corynebacterium diphtheriae* that mediates bacterial attachment to human pharyngeal epithelial cells. SpaA pilus polymerization requires pilin-specific sortase SrtA. The goal of my project is to reconstitute SrtA-catalyzed SpaA polymerization *in vitro*, with the aim of studying SrtA kinetics and sortase-substrate specificity as well as obtaining a co-crystal structure of SrtA and SpaA. Structural analysis of sortase SrtA reveals the presence of a “lid” made of a conserved DPW motif. It is thought that the lid controls SpaA access to the SrtA catalytic site. We hypothesized that a recombinant sortase SrtA with both D and P residues mutated to G (SrtA-DW→G) would be active *in vitro* as these mutations unblocked the active site. To test this, I expressed the wild-type and mutant sortase proteins in *Escherichia coli* cells and purified them from clear lysates by nickel-column purification, followed by dialysis. Both wild-type and mutant enzymes were incubated with recombinant SpaA for up to 96 hours at 37°C. It was observed that the SrtA-DW→G enzyme, not the wild-type, was able to polymerize SpaA subunits, indicating that these two residues may play a role in controlling the active site of sortase SrtA. Now that we have observed pilus polymerization, the next step would be to analyze its kinetics and substrate specificity, and possibly obtain the co-crystal structure of Srt A DW->G and SpaA.

## ABSTRACT

### Analysis of Activated Microglia/Macrophage in the Acute Phase (3 days) Response to Cerebral Ischemia

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Sponsored by: Jaroslaw Aronowski, MD, PhD, Xiurong Zhao, MD, Department of Neurology

Supported by: NNINIH-NINDS-R01NS084292; The University of Texas at Houston Medical School - Office of the Dean

Key Words: stroke, RXRa, microglia, macrophage, inflammation

A complex set of neuroinflammatory reactions triggered by tissue injury represent an important component of ischemic stroke pathobiology. These responses include, but are not limited to, microglia activation and blood-derived macrophage and neutrophil infiltration into brain parenchyma. Retinoid X receptor alpha (RXR $\alpha$ ) and peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) form a heterodimer that by binding to a specific responsive element regulates the transcription of many genes targets including several that are associated with anti-oxidative activities in microglia and macrophages. During acute inflammatory responses, activated microglia and macrophages may have both beneficial and detrimental consequences. Activated microglia via phagocytosis-mediated cleanup eliminate from the site of injury cytotoxic and pro-inflammatory debris apoptotic cell (e.g. neutrophils), but can also produce pro-inflammatory cytokines and proteolytic enzymes that could disrupt the blood-brain barrier leading to edema and hemorrhagic transformation. Further study of these responses may allow for a better understanding of the post-stroke inflammatory mechanisms. The 60 min transient tandem middle cerebral artery (MCAO)/common carotid (CC) occlusion (MCA/CCAo) model of ischemic stroke in C57/BL male mice (2 months old) was employed to generate ischemic damage that models stroke in humans. Fifteen mice were employed. Nine mice were genetically engineered to selectively lack RXRa in microglia/macrophages (MM $\Phi$ ), Lys-RXR $\alpha$ -KO and seven mice were the control wild-type (WT) mice. The mice were euthanized 3 days after MCA/CCAo to observe for differences in the acute phase response between the Lys-RXR $\alpha$ -KO and WT. Brains cryo-sectioned into 10  $\mu$ m coronal sections were treated with antibodies against CD68 and Ly6G to mark MM $\Phi$  and neutrophil infiltration, respectively. Staining was visualized using fluorescent microscope and Metamorph software. There was no significant difference ( $p=.961$ ) in the number of microglia/macrophage per ipsilateral hemisphere between the Lys-RXR $\alpha$ -KO ( $M=594$ ,  $SD=95.04$ ) and the WT ( $M=570.67$ ,  $SD=731.69$ ). No statistical difference was found in the infarct volume between the Lys-RXR $\alpha$ -KO and WT mice. There was also no significant difference in the size of the activated MM $\Phi$  ( $p=.100$ ) between the Lys-RXR $\alpha$ -KO mice and WT. The average size of the activated MM $\Phi$  was 275.17  $\mu$ m ( $SD=165.34$ ) and 113.91  $\mu$ m ( $SD=75.98$ ) in Lys-RXR $\alpha$ -KO mice ( $n=3$ ) and WT ( $n=5$ ), respectively. There was a significant decrease ( $p<0.01$ ) in the number of infiltrating neutrophils in the RXR $\alpha$ -knockout as compared to WT mice ( $M=346.25$ ,  $SD=164.88$  vs.  $M=1794.33$ ,  $SD=593.95$ ). Further study is required to understand the relation of the RXR gene to activated microglia/macrophages.



# ABSTRACT

## Epigenetic and IL-10 Mediated Regulation of Colitis

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Sponsored by: Jeremy S. Schaefer, PhD, Department of Diagnostic & Biomedical Sciences

Supported by: Career Development Award No. 3627 from the Crohn's and Colitis Foundation of America; NIH grants DK035566 and AI100159

Key Words: Inflammation, Epigenetics, Roquin-1, IBD

**Background:** Epigenetics refers to the heritable phenotypic changes to gene expression that are not encoded by the underlying DNA sequence. Primary mediators of this include DNA methylation and histone modifications, such as methylation, acetylation, phosphorylation, and ubiquitylation. Thus, these epigenetic modifications are important for development. Evidence indicates that perturbations of epigenetic marks can lead to disease. Inflammatory bowel disease (IBD) is a collection of inflammatory conditions characterized by chronic inflammation within the gastrointestinal tract. Although the causes of IBD are not well understood, evidence suggests that a combination of genetic, environmental, epigenetic, and microbial factors influence the course of disease. Previous studies have shown that an interconnected regulatory pathway exists between interleukin 10 (IL-10), an anti-inflammatory cytokine, and Roquin-1 (*Rc3h1*), a RING finger ubiquitin ligase with immune functions. In IL-10 knockout (IL-10<sup>-/-</sup>) mice, a mouse model that develops a chronic intestinal inflammation that mimics aspects of IBD, Roquin-1 expression was decreased in the inflamed intestinal tract. In the present study, we investigated the epigenetic profile of IL-10<sup>-/-</sup> mice as it relates to Roquin-1 to gain further insight into the regulation of intestinal inflammation.

**Methods:** The EL4 thymoma cell line and mucosal biopsies from IL-10<sup>-/-</sup> mice and control BALB/c mice were used to investigate the epigenetic regulation of the *Rc3h1* gene in relation to IL-10 signaling and intestinal inflammation. Chromatin immunoprecipitation (ChIP) followed by qPCR was used to examine the epigenetic marks in IL-10 mouse tissue and cells.

**Results:** In IL-10<sup>-/-</sup> mouse colons, the *Rc3h1* locus had increased methylation and reduced ubiquitylation. In contrast, the *Rc3h1* locus is poorly methylated and highly ubiquitylated in BALB/c colons.

**Conclusions:** These results demonstrate that the *Rc3h1* locus is transcriptionally silenced during inflammation. This supports a role for *Rc3h1* in the maintenance of immune homeostasis.

# ABSTRACT

## Contractility of Small Intestines in Rats with Induced Edema

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*Class of 2015*

Sponsored by: Karen Uray, PhD, Department of Pediatrics

Supported by: Karen Uray, PhD, Department of Pediatrics

Key Words: Edema, Intestines, Transit

**Background** Intestinal edema results in decreased contractility of smooth muscle, slowing down intestinal transit. Therefore, we hypothesize that longitudinal and cyclic forces may vary in intestines with different degrees of edema. We sought to examine the relationship between the transit measurement and these two forces.

**Methods** Varying degrees of intestinal edema were induced by partial occlusion of the superior mesenteric vein and administration of 20cc, 40cc and 80cc edema. After injecting non-absorbable fluorescent dye, distal small intestines were collected after 6h of induced edema and hung in organ baths filled with Krebs solution, gassed with O<sub>2</sub> and heated to 37 °C. 4 segments of each tissue were hung separately and stretched longitudinally. The contractions of intestines were monitored by a sensor and recorded in a Powerlab data acquisition software. Each segment was allowed to contract freely, achieving equilibrium after 30 minutes. After recording baseline data, two segments were treated with vehicle while the other two segments were treated with tetrodotoxin. Integral, integral relative to minimum, average cyclic height, average cyclic minimum and average cyclic frequency were calculated using built in functions in the software and normalized to cross-sectional area of each segment. Transit measurement was done by evaluating distribution of fluorescence in the small intestines.

**Results** Integral relative to minimum presents an identical trend as intestinal transit measurement by degrees of edema from control to 80cc, decreasing as dose increases. Tone, instead, increased as dose increased.

**Conclusion** Integral relative to minimum may serve as an indicator for intestinal transit, but it was not clear if longitudinal force alone or together with cyclic force contributes to the measurement.

## ABSTRACT

### The Role of Crh, an Hpr Homologue, on Expression of the *Bacillus anthracis* Virulence Regulator AtxA

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Class of 2016

Sponsored by: Theresa M. Koehler, PhD, Department of Microbiology and Molecular Genetics

Supported by: Molecular Basis of Infectious Disease (MBID) Training Grant, NIH T32 AI59048 and T32 AI55449-09

Key Words: *Bacillus anthracis*, carbon catabolite repression, histidine phosphocarrier protein

Virulence gene expression by *Bacillus anthracis*, the causative agent of anthrax, is controlled by a key regulatory protein "AtxA". This master virulence regulator positively controls transcription of the anthrax toxin genes and the capsule biosynthetic operon. The signals and factors that affect expression of the *atxA* gene are not well established. Recent data suggest roles for the histidine phosphocarrier protein (Hpr) and the carbon catabolite protein A (CcpA) in transcription of *atxA*. Deletion of genes encoding Hpr and/or CcpA results in decreased *atxA* transcript levels. In many bacteria, Hpr plays an essential role in metabolism by connecting sugar import and carbon catabolite repression activities within the cell. When Hpr is phosphorylated at serine 46, Hpr forms a complex with the carbon catabolite protein A (CcpA) to influence transcriptional regulation by CcpA. *B. anthracis* carries a gene, *ptsH2*, encoding an Hpr homologue, Crh (Catabolite repression HPr) which has a serine at residue 46. I hypothesized that Crh contributes to control of *atxA* transcription. Using a temperature-sensitive vector and homologous recombination, I constructed a *B. anthracis ptsH2*-null mutant in a strain carrying a transcriptional reporter, *atxA-lacZ*. The parent and mutant strains had similar growth rates in medium conducive for *atxA* expression. I performed beta-galactosidase assays to compare the activity at the promoter of *atxA* in the two strains. Preliminary data showed a 1.4 fold increase in activity at the *atxA* promoter in *B. anthracis ptsH2*-null mutant compared to the parent. These data suggests that Crh affects *atxA* transcription. If these results prove to be reproducible, future work will test for *crh* - *hpr* synergy and protein interactions between Crh, Hpr, and CcpA.

## ABSTRACT

### Down-Regulation of ENTs Exacerbates Bleomycin-Induced Pulmonary Fibrosis

NGOC-BAO LE

Stanford University

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Sponsored by: Michael R. Blackburn; Department of Biochemistry and Molecular Biology

Supported by: Michael R. Blackburn; Department of Biochemistry and Molecular Biology

Key Words: equilibrative nucleoside transporters (ENT), adenosine, pulmonary fibrosis

**Background:** Pulmonary fibrosis occurs when lung tissue becomes damaged and scarred. Adenosine, a signaling nucleoside, is thought to play a part in the development of this disease. Adenosine is produced following tissue injury, particularly ischemic and hypoxic injuries. As result of hypoxia, cells release ATP and other adenine nucleotides that are converted to extracellular adenosine, which initiates signaling cascades through activation of adenosine receptors. In acute injury, this hypoxic adenosine response activates pathways that promote tissue adaptation. In contrast, if elevated extracellular adenosine levels are sustained beyond the acute injury phase, adenosine responses can become detrimental by activating pathways that promote tissue injury and fibrosis. One way in which adenosine is regulated following injury is through equilibrative nucleoside transporters (ENTs), which are bi-directional facilitated transporters. Elevations in extracellular adenosine occur following adenine nucleotide release and degradation during cellular distress such as hypoxia. This promotes the net flow of adenosine from outside to inside the cell. The purpose of this study is to determine whether the inhibition or down regulation of ENTs causes extracellular adenosine levels to remain elevated past the acute injury phase, which, in turn, leads to pulmonary fibrosis.

**Methodology:** To characterize differences in ENT expression in normal versus fibrotic lungs, protein samples from the lungs of mice treated with PBS (control) or bleomycin (to induce pulmonary fibrosis) were collected and analyzed by Western blot. Bronchoalveolar lavage fluid was collected and evaluated for extracellular adenosine levels using liquid chromatography. Pulse oximetry data was collected as an indicator of lung function. To evaluate the effects of ENT inhibition on adenosine levels and pulmonary fibrosis, mice were exposed to bleomycin and treated with dipyridamole, an ENT inhibitor. Western blot analysis, pulse oximetry, and immunohistochemistry studies were performed on samples from these mice.

**Results:** Mice with bleomycin induced pulmonary fibrosis were found to have lower levels of ENT protein, higher levels of extracellular adenosine, and impaired lung function compared to PBS injected control mice. Mice exposed to bleomycin and treated with dipyridamole displayed even higher levels of extracellular adenosine, worse lung function, and higher levels of fibrotic tissue than mice exposed to PBS alone or bleomycin alone.

**Conclusions:** ENTs serve an essential role in the development of pulmonary fibrosis. Downregulation of ENTs resulted in persistence of elevated extracellular adenosine following injury, which may promote signaling that leads to the development of pulmonary fibrosis.

## **ABSTRACT**

### **Determination of Degree of Compound Formation in Indomethacin-Phosphatidylcholine Complexes**

TONY LI-GENG

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Sponsored by: Lenard M. Lichtenberger, PhD, Department of Integrative Biology and Pharmacology

Supported by: NIH SBIR grant R44 HD061132 to PLx Pharma LLC, Lenard Lichtenberger, PhD; The University of Texas at Houston Medical School – Office of the Dean

Key Words: indomethacin, phosphatidylcholine, column chromatography

Indomethacin is a non-steroidal anti-inflammatory drug commonly used to relieve pain and reduce inflammation. A side effect of indomethacin is gastrointestinal toxicity, thus preventing many patients from taking advantage of the drug's analgesic and other beneficial properties. A complex in which Indomethacin associates with Phosphatidylcholine (PC) has been shown to reduce gastrointestinal side effects in patients, thus widening the range of patients who can use indomethacin. Previously, computational simulations have demonstrated that Indomethacin forms ionic and hydrophobic associations with PC. This study attempts to confirm presence of interactions between indomethacin and PC using column chromatography. Indomethacin-PC samples are run through a G-10 column and the elution fluid assayed for Indomethacin and PC. The results showed lab-made indomethacin-PC created by vaporizing the two in acetone solution formed some complex, all of which remained intact through the G-10 column. For three samples from Core RX Pharma derived with mannitol or sucrose sugars, some indomethacin elutes after the PC but before free indomethacin run through the G-10 column normally does. Additionally, the complex does not appear on elution profiles when the samples had been put into solution for more than one day. This data suggests the lab-formed indomethacin-PC forms the strongest complex while the sugar infused samples form weaker complexes and also have a shelf life, once put into solution, of less than one day. These results are relevant in understanding the mechanism by which indomethacin-PC interacts with the gastrointestinal tract and how these interactions affect the efficacy of indomethacin-PC in reducing gastrointestinal side effects.

## **ABSTRACT**

### **ADHD Severity as a Predictor of Comorbid Symptomatology in Children with Autism Spectrum Disorders**

*EMILY MITARO*

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Sponsored by: Deborah A. Pearson, PhD, Department of Psychiatry and Behavioral Sciences

Supported by: Deborah A. Pearson, PhD, Department of Psychiatry and Behavioral Sciences;  
The University of Texas at Houston Medical School – Office of the Dean

Key Words: Autism, ADHD, psychiatric comorbidity

Psychiatric comorbidity has been shown to be highly prevalent in individuals with Autism Spectrum Disorders (ASD). In children with ASD, Attention Deficit/Hyperactivity Disorder (ADHD) symptomatology is present in particularly high proportions relative to other psychiatric disorders. However, it remains unknown as to whether the severity of ADHD symptoms may pose as a risk factor for additional comorbid psychiatric diagnoses in this population. The aim of this study was to examine both ADHD and ASD symptom severity as predictors of additional comorbid DSM-IV diagnoses in children and adolescents with ASD. It was hypothesized that children experiencing greater severity of ADHD, rather than ASD, symptoms would be at higher risk for comorbid psychiatric symptomatology. Of the 99 children and adolescents who participated in the study (ages=6-13 years, males=78, females=21), all met criteria for ASD and 85 additionally met criteria for ADHD. ASD diagnosis was determined using the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). ADHD and other psychiatric conditions were diagnosed using the Diagnostic Interview for Children and Adolescents-Fourth Edition (DICA-IV) and the Child Behavior Check List (CBCL). Assessment of IQ was completed using the Stanford Binet-Fifth Edition (SB-5). Results of a general linear model showed that among children with comorbid ASD and ADHD, ADHD severity was positively and significantly related to number of comorbid diagnoses,  $F(1,95)=9.004$ ,  $p=.003$ , and reported levels of CBCL syndrome severity  $F(8,88)=23.79$ ,  $p=.001$ , while no significant relationship was found of ASD severity (all  $p>.05$ ). This indicates that psychiatric comorbidity in children with ASD may be more strongly associated with the severity of ADHD rather than ASD symptoms. Further research is required to confirm these findings.

## ABSTRACT

### AHCC Modulates Hypertension Via the Nitric Oxide Signaling Pathway in Rats

LORD MVOULA

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Class of 2014

Sponsored by: Marie Francoise Doursout, PhD, Department of Anesthesiology

Supported by: Marie Francoise Doursout, PhD, Department of Anesthesiology; The University of Texas at Houston Medical School – Office of the Dean

Key Words: AHCC, Hypertension rats. Nitric Oxide

**Background:** Hypertension and cancer are amongst the top 20<sup>th</sup> leading causes of death worldwide. The work of previous scientists suggest that most patients with either hypertension and/or cancer have endothelial dysfunction which is primarily a result of impaired nitric oxide (NO) availability secondary to oxidative stress production. Although inflammation/oxidative stress in diseases such as cancer or hypertension has been, and is still being treated by conventional medicine; our research provide strong evidence that direct Active Hexose Correlated Compound (AHCC, Amino Up), produced from the mycelia of shiitake inhibit oxidative stress in hypertension.

**Experimental Design:** Six spontaneously hypertensive (SHR; n=6) rats and their counterparts Wistar Kyoto (WKY; n=6) rats were surgically instrumented to continuously record mean arterial blood pressure (MAP) and heart rate (HR). Following surgical recovery, SHR and WKY received AHCC (10%) in drinking water for 3 days. MAP, HR and NO production were recorded at baseline (prior AHCC treatment) and 3 days following AHCC treatment.

**Results and conclusions:** Our data show that AHCC decreased SHR-induced hypertension by 35 % whereas MAP remained unchanged in WKY control rats. Furthermore, AHCC partially restored NO production to baseline conditions and also inhibits edema formation in SHR rats. Additional experiments are being conducted to further elucidate oxidative stress in SHR rats in the presence and in the absence of AHCC. In conclusion, our preliminary data demonstrate that AHCC might be an effective therapeutic agent in diseases inducing endothelial dysfunction, e.g. hypertension, especially when the NO signaling pathway is impaired.

## **ABSTRACT**

### **A Retrospective Study of The Aesthetic Surgery Resident Clinic**

*MAEGAN NOLEN*

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*Class of 2016*

Sponsored by: David J Wainwright MD, Department of Surgery

Supported by: David J Wainwright MD, Department of Surgery; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Cosmetic resident clinic, retrospective, cosmetic surgery

**Introduction:** The aesthetic surgery clinic overseen by UT Health Sciences Medical School acts as source of educational training to the residents and fellows, while simultaneously benefitting patients financially. The use of cosmetic clinics to train plastic surgery residents has been accepted as a highly effective tool for educating future plastic surgeons. This retrospective study was developed to pinpoint trends and evaluate the patient population receiving care from the cosmetic surgery residents. **Methods:** After reviewing all pertinent literature surrounding cosmetic resident clinics, a database was subsequently created to categorize all patients seen by the residents in the last five years. The database is separated into several categories including: patient demographics, visit characteristics, problem characteristics, surgery characteristics, and a final result. **Results:** To date there have been 34 patients entered into the database representing a range of four months. A total of 186 appointments were made with 62% (116) having arrived, 12% (23) did not show, and 25% (47) cancelled. The average age was 42, and 26% (9) of patients had surgical procedures performed. The most common surgical procedures performed were: liposuction of abdomen (1), liposuction of flanks (2), and liposuction of the face and medial/lateral legs (3). **Conclusions:** The database is incomplete, however with time the complete database will allow conclusions to be drawn as well as showing categorical trends.



## **ABSTRACT**

### **Characterization of PC3 Metastatic Behavior Under Shear Stress**

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Supported by: The State of Texas Emerging Technology Fund, The ASH Scholar Award, NIH 1K01DK092365-04

Key Words: Invasion, YAP, PC3, cancer, metastasis

Interstitial fluid flow causes biophysical force and surrounds the cells of multicellular organisms. Fluid frictional force plays an integral role in regulating the microenvironment that surrounds healthy cells, as well as cancer cells. Shear stress can regulate cellular activity such as cytoskeletal reorganization, motility, and internal signaling. However, the intrinsic pathway of mechanotransduction is poorly understood. Recently, YAP (yes associated protein) and TAZ, both transcriptional coactivators, have been found to mediate cancer cell motility. Without proper deactivation from the Hippo tumor suppressor pathway through cytoplasmic sequestration, YAP interacts with the TEAD domain, which can initiate metastasis. While YAP has emerged as a mechanosensitive oncoprotein, its role in prostate cancer has not been thoroughly characterized; however, in cancerous prostate tissue samples, YAP and TAZ upregulation is evident, displaying their sensitivity to mechanical forces in the tumor microenvironment, which leads to increased cellular motility. In order to visibly illustrate metastatic behavior, PC3 cells were seeded at a density of 100,000 cells/10  $\mu$ l onto 3.0 mg/ml Rat tail Type 1 collagen matrices and sheared for 24 hours. Both static and shear cell samples were fixed with 2% glutaraldehyde in PBS for 1 hour, stained with 0.01 % toluidine blue, and counted for quantification. Evaluation of shear conditions in comparison to static conditions yielded visible evidence of significantly higher invasiveness. In view of activation in response to shear stress, further investigation into internal mechanotransductive cell regulators responsible for cancer cell metastasis is urgently needed.

## ABSTRACT

### Regulation of *Borrelia burgdorferi* Surface Lipoproteins: Major Virulence Factors of Lyme Disease

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Sponsored by: Steven J. Norris, PhD, Department of Pathology and Laboratory Medicine

Supported by: NIH Grant 5 T32 AI 55449-9

Key Words: Lyme disease, *Borrelia burgdorferi*, *vlsE*

Lyme disease is a tick-transmitted bacterial infection caused by spirochete bacteria in the genus *Borrelia*, and *Borrelia burgdorferi* is the main pathogen that causes the disease in North America. Although *Borrelia* does not secrete any known toxins, it causes musculoskeletal, neurologic, and cardiovascular symptoms in later stages of Lyme disease. One of the major proteins involved in this pathogen's ability to evade the host's immune response is the VlsE surface lipoprotein that is expressed on the outer surface of the outer membrane. The gene for VlsE is located on the *vls* locus along with 11-15 silent cassettes, which undergo recombination with the *vlsE* expression site leading to antigenic variation. Another outer surface lipoprotein, OspC, also undergoes recombination, but does not utilize the antigenic variation mechanism. . Understanding the regulation of VlsE and OspC can be useful for developing improved treatment therapies for Lyme disease. It is hypothesized that a phosphoenolpyruvate-phosphotransferase system (PEP-PTS) regulates *vlsE* and *ospC* expression through the PtsG protein since this system regulates virulence in other gram-positive and gram-negative organisms. To test this hypothesis, we grew wild type, *ptsG* mutant, and *ptsG* complement strains of *B. burgdorferi* culture, isolated RNA from them at different time intervals, and utilized quantitative-reverse transcriptase-PCR to analyze *vlsE* and *ospC* expression. According to the results, the mutant and complemented strains were found to have more *vlsE* transcripts and fewer *ospC* transcripts relative to the wild type strain at all time points. There was also less VlsE protein in the mutant and complemented strains relative to the wild type strain, which was most likely due to uneven protein concentrations. The effect of topoisomerase inhibitors, specifically nalidixic acid and coumermycin A1, on *vlsE* expression was also tested, and results showed that nalidixic acid increases *vlsE* transcript levels while coumermycin A1 has no effect on *vlsE* expression. Some of these results were contradictory to previous studies done in our lab so further validation of these results is needed.

## **ABSTRACT**

### **Enhancing Mesenchymal Stromal Cell Anti-Inflammatory Behavior Through Biomechanical Force**

*KATHERINE PRICE*

*Rice University*

*Class of 2016*

Sponsored by: Pamela L. Wenzel, Department of Pediatric Surgery

Supported by: The State of Texas Emerging Technology Fund, The ASH Scholar Award, NIH 1K01DK092365-04; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Mesenchymal Stromal Cells, Inflammation, Biomechanical Force

It has been shown that mesenchymal stromal cells (MSCs) have numerous clinical applications. Of specific interest to our lab is the ability of MSCs to suppress chronic and acute inflammation. Importantly, MSC immunomodulatory capacity is not innate and must be induced via a process called licensing, which can occur through exposure to various inflammatory cytokines or, as determined by unpublished studies in the Wenzel lab, through the application of biomechanical force, such as fluid shear stress. We applied a combination of laminar shear stress and hydrostatic pressure to MSCs to test the hypothesis that exposure to both pressure and shear can more potently amplify the immunomodulatory function of MSCs. Cells were exposed to pressure and shear stress simultaneously for 3 hours and gene expression was analyzed. Our findings suggest a combination of shear stress and pressure licenses MSCs more effectively than either force alone. We also found that an upper threshold of pressure exists, after which the effectiveness of the licensing technique begins to decrease. In future work, our studies are designed to explore the possibility that controlled application of shear stress and pressure could be an innovative method for enhancing MSC immunomodulatory potency.

## **ABSTRACT**

### **The Opioid-Sparing and Analgesic Effects of IV Acetaminophen in Craniotomy: A Prospective, Randomized, Placebo-Controlled, Double-Blind Study**

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*Class of 2016*

Sponsored by: Carin A. Hagberg, MD, Department of Anesthesiology

Supported by: Carin A. Hagberg, MD, Department of Anesthesiology; The University of Texas at Houston Medical School – Office of the Dean

Key Words: IV Acetaminophen, Craniotomy, Opioid-Sparing, Analgesic

Background: Patients have had numerous side effects after craniotomy procedures including post-operative nausea vomiting (PONV), opioid dependence, and opioid-induced respiratory depression. IV acetaminophen has been well tolerated in clinical trials and lacks many of the side effects that are associated with other opioid and non-opioid analgesics. The use of IV acetaminophen has the potential to reduce narcotic requirements and the associated risks while allowing for a rapid postoperative neurological assessment, greater patient satisfaction, and superior pain control than with opioid therapy alone.

Primary Aim: Establish the beneficial analgesic and opioid-sparing effect of IV acetaminophen in patients undergoing craniotomy for intracranial mass resection by determining the reduction in 24-hour postoperative morphine use.

Methods: This is a randomized, double-blind, placebo-controlled study comparing IV acetaminophen to a placebo. One hundred patients presenting for elective supratentorial craniotomy for intracranial mass resection will be enrolled in the study. Patients randomized to Group 1 received doses of 1g of IV acetaminophen at the scheduled time intervals; patients randomized to Group 2 received 100cc of normal saline as a placebo at the same time intervals. These formulations were prepared in identical, unlabeled bags so that the patients, attending anesthesiologists, surgeons, postoperative observers and all other study personnel were blind to which drug is being administered. Pain scores were assessed using the visual analog scale (VAS) upon entering the PACU or upon extubation in PACU (0 hours), and then again at 1, 2, 4, 8, 12, 16, 20, and 24 hours post-operatively. Post-operative nausea was recorded on a 10 cm numeric rating scale (NRS) at the same time intervals, with 0 indicating no nausea and 10 indicating severe nausea.

Results: Currently, 43 of 100 patients have been recruited for the study. Due to the ongoing recruitment and double-blinded nature of this study, quantifiable results are not available at this time. We are therefore unable to make any conclusions at this time.

## ABSTRACT

### Discovering New Antibiotics Targeting Bacterial Isoprenoid Biosynthesis

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Sponsored by: Heidi B. Kaplan, PhD, Department of Microbiology and Molecular Genetics

Supported by: Molecular Basis of Infectious Disease NIH Training grant 5T32AI055449-09

Key Words: Methylene erythritol phosphate, mevalonate, antibiotic resistance, high-throughput screen, fluorescence

Antibiotic resistance is a serious medical concern since the extensive use of antibiotics has selected for pathogens resistant to many current antibiotics. There is a major need to identify new antibiotics that act on previously unutilized targets. We are developing a novel high-throughput screen for antibiotics that target the bacterial isoprenoid biosynthesis pathway. All organisms require isoprenoids for growth. Bacteria and humans use different biosynthetic pathways; bacteria commonly use the methylerythritol phosphate (MEP) pathway, whereas humans use the mevalonate (MVA) pathway. Fosmidomycin (FSM) is the only known MEP pathway inhibitor; it is not a useful antibiotic due to uptake problems. Our screen will identify FSM-like compounds that inhibit the bacterial MEP pathway, but do not affect the human MVA pathway. For the screen two *E. coli* strains will grow in the same wells of a 96-well plate. One strain will contain both the MEP and MVA pathways and express a green fluorescent protein; the other strain will contain only the native MEP pathway and express a red fluorescent protein. The drugs of interest will kill single-pathway strains, and allow dual-pathway strains to live.

After several unsuccessful attempts to clone the MVA pathway genes, I acquired plasmid pBba25C that contained the yeast MVA pathway. I transformed this plasmid into three *E. coli* strains and studied their growth. The optical density at 600 nm was measured every 20 min for 20 hr at 37°C with shaking in a plate reader. Triplicate sample wells contained one strain with or without the plasmid that was grown with 1mM IPTG and with or without 5 mM FSM. IPTG allows transcription of the plasmid-encoded MVA genes, which are controlled by a *lac* promoter. I hypothesized that without FSM both strains would grow, however in wells containing both IPTG and FSM I expected the MEP strains (with no plasmid) to die and the plasmid-containing strains to grow. My data did not agree with this hypothesis. I detected similar limited growth in both strains exposed to IPTG and FSM. I will repeat this growth experiment with increased concentrations of both FSM and IPTG. I expect that this will more effectively inhibit growth of the MEP-pathway strains and increase MVA gene transcription allowing for more robust growth in the plasmid-containing dual pathway strain.

## ABSTRACT

### Determining the Components of the Wnt Signaling Pathway that Regulate Immune Responses in *C. elegans*

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Class of 2015

Sponsored by: Ransome V. van der Hoeven, PhD, Department of Diagnostic and Biomedical Sciences

Supported by: Ransome V. van der Hoeven, PhD, Department of Diagnostic and Biomedical Sciences

Key Words: Wnt signaling, antimicrobial response, *C. elegans*, *S. aureus*

Wnt proteins are secreted, lipid-modified glycoproteins that control many aspects of development via the activation of the canonical Wnt signaling pathway, which is highly conserved in organisms ranging from invertebrates to mammals. This pathway mainly regulates the expression of specific target genes through the effector protein  $\beta$ -catenin. It has been previously shown that  $\beta$ -catenin regulates an immune response in the intestine of *Caenorhabditis elegans*. Therefore, we hypothesized that components of the canonical Wnt signaling pathway also play a role in the regulation of the immune response in *C. elegans* during infection. In this study, we observed changes in Wnt ligand expression, and we further identified components of the degradation complex (*gsk-3* and *pry-1*) and a Wnt inhibitor (*cam-1*) that negatively regulate the antimicrobial response in the worms to *Staphylococcus aureus*. Through quantitative RT-PCR analysis, we observed that the expression of four Wnt proteins (*cwn-1*, *cwn-2*, *egl-20*, and *lin-44*) in *C. elegans* was significantly upregulated in response to *S. aureus*. In addition, we performed quantitative RT-PCR analysis to study expression levels of three antimicrobial proteins regulated by  $\beta$ -catenin (*fmo-2*, *ilys-3*, and *clec-60*) using intestinal-specific RNAi knockdowns in the *vha6::sid-1* worm strain. Our results showed a significant increase in antimicrobial expression with the *gsk-3*, *cam-1*, and *pry-1* knockdowns, and a significant decrease in expression in the *lin-17* and *lin-44* knockdowns. These results were further confirmed by microscopic analysis of a transgenic worm strain expressing the antimicrobial protein *clec-60* fused to green fluorescent protein. Finally, data from killing assays showed that *cam-1*, *gsk-3*, and *pry-1* knockdowns were more resistant to the pathogen as compared to the vector control, while *lin-17* and *lin-44* were more susceptible.

## ABSTRACT

### *Caenorhabditis elegans* and *Candida albicans*: Screens of Factors Important for Virulence

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Sponsored by: Danielle A. Garsin, PhD, Michael C. Lorenz, PhD, Department of Microbiology & Molecular Genetics

Supported by: Molecular Basis of Infectious Diseases (MBID) Training Grant, NIH T32 AI59048 and T32 AI55449-09

Key Words: *Enterococcus faecalis*, *Candida albicans*, *Caenorhabditis elegans*, virulence

One in 25 patients develop a hospital-acquired illness, with *Enterococcus* and *Candida* species as the third and fourth most common infectious agents. The bacterium, *Enterococcus faecalis*, and the fungus, *Candida albicans*, while opportunistic pathogens, are also commensal organisms found in overlapping niches in the human body. *Caenorhabditis elegans*, a nematode, is a model organism for virulence and immune-response study. Previous research showed that *E. faecalis* inhibits hyphal morphogenesis and biofilm formation of *C. albicans* in *C. elegans*, causing reduced killing. One of my projects aimed to determine which *C. albicans* genes affect susceptibility to biofilm inhibition by *E. faecalis*. A biofilm assay was used to conduct screens of mutant libraries, where *C. albicans* mutants were grown with and without supernatant from cultures of *E. faecalis*. Results identified 24 *C. albicans* mutants that block inhibition of biofilm formation in the presence of *E. faecalis* supernatant. Interestingly, the genes have functions related to cell wall stress and hyphal morphogenesis. Next steps in this research include screening additional libraries for more *C. albicans* genes, and experiments to characterize any changes to the cell walls of the *C. albicans* mutants already identified.

In a second project, I performed a screen to identify *C. elegans* collagen genes that affect susceptibility to *E. faecalis* infection. The rationale was that collagen genes, which encode for the biosynthesis of the cuticle, were highly regulated during infection in published transcriptome studies. Additionally, the Garsin lab had identified a mutant in a gene with potential roles in cuticle formation as being susceptible to *E. faecalis*. Screens of *C. elegans* collagen genes were performed using RNAi and susceptibility assays. Nematodes in which col-12, col-77, and col-181 were knocked-down, have decreased survival compared to nematodes fed empty vector, showing that these genes may be important for resisting *E. faecalis* infection. Next, these RNAi knockdowns will be tested for susceptibility to other bacterial and fungal pathogens.

## ABSTRACT

### The *empA* gene Complementation of TX82 $\Delta$ *empA*

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Sponsored by: Barbara E Murray, MD, Department of Internal Medicine

Supported by: NIH training grant T32 AI55449 (09/15/2005-07/31/2015)

Key Words: Complementation, *Enterococcus faecium*, Pilus Formation, Counter-Selection

*Enterococcus faecium* is a commensal bacteria of the human GI tract. *E. faecium* is a gram-positive bacteria and also an opportunistic pathogen, often infecting immunosuppressed patients in a hospital setting. Frequent infections caused by *E. faecium* include catheter-associated Urinary Tract Infections (UTIs), surgical site infections, and endocarditis. It was previously shown by Murray et al. 2010 that a deletion of the EmpABC operon in *E. faecium* TX82, which encodes for pili formation, causes reduced biofilm formation of the TX82 $\Delta$ *empABC* mutant compared to TX82. Of the three genes on the EmpABC operon (*empA*, *empB*, and *empC*) *empA* was shown, upon deletion, to cause significantly more reduction in biofilm formation than either the TX82 $\Delta$ *empB* or TX82 $\Delta$ *empC* mutants. Complementation was necessary to verify the absence of a secondary mutation causing the phenotypic change in biofilm formation observed in TX82 $\Delta$ *empA*. PCR was used to isolate the gene of interest, *empA* (~3,400 bp) with primers located about 500 bp on either side of the gene aid in the later recombination. The gene was then ligated into the TOPO vector and electroporated into *E. coli* 1000. The TOPO vector and the pHOU1 vector were cut with the same restriction enzymes and subsequent ligation of the PCR fragment and the digested pHOU1 vector was perform. The pHOU1 vector containing the insert was then electroporated into CK111, a strain of *Enterococcus faecalis* which has the repA gene *in trans*. CK111 was than conjugated with TX82 $\Delta$ *empA* and the transconjugants were selected on a selective media. The resulting transconjugants were than plated on p-chloro-phenylalanine plates which selects for the excision of the pHOU1 vector from the chromosome, but leaves the *empA* gene. pHOU1 contains the *pheS* gene which confers sensitivity to p-chloro-phenylalanine. Plating on p-chloro-phenylalanine provides a counter-selectable marker and provides a clean insertion *in cis*. Intragenic and intergenic PCRs were preformed, along with sequencing to verify the TX $\Delta$ *empA* mutant for presence of *empA*. Analysis of the TX $\Delta$ *empA*::*empA* complement with a growth curve and biofilm assay showed the wild-type TX82 and the complement TX $\Delta$ *empA*::*empA* perform similarly. Further testing is required to confirm the complement TX $\Delta$ *empA*::*empA* was created but the preliminary analysis indicates the complementation of TX82 $\Delta$ *empA* was successful.



## **ABSTRACT**

### **Maryland Model of Closed-Head Concussive Traumatic Brain Injury: Blood Brain Barrier Permeability and Behavior**

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Sponsored by: Raymond J. Grill, PhD, Department of Integrative Biology and Pharmacology

Supported by: Mission Connect and the Gillson-Longenbaugh Foundation; The University of Texas at Houston Medical School – Office of the Dean

Key Words: Maryland Model, Traumatic Brain Injury, Blood Brain Barrier, Motor Function

Traumatic brain injury (TBI) is the leading cause of death worldwide for people under the age of 45. While motor vehicle accidents and sports injuries are two common causes of TBI in humans, there is a clear need for animal models that replicate human clinical injury pathologies. The Maryland Model of TBI produces the anterior-posterior plus sagittal rotational acceleration that is commonly seen in motor vehicle accident and sport injury-related human TBI. It produces horizontal impact, closed-head concussive TBI to the anterior cranium with minimal skull fracture. We sought to characterize this novel rat model of TBI by investigating blood brain barrier (BBB) permeability and behavior at acute and chronic time points. We hypothesized that this model would produce sustained BBB dysfunction and behavior deficits. Acute phase BBB permeability was assessed using an exogenously delivered 10K molecular weight dextran-conjugated to an infrared dye given 30 minutes prior to sacrifice at 24 hours post-injury in five injured and four sham rats. In 14 injured and 14 sham rats given a 16 day survival time, vestibulomotor function and spontaneous motor activity were assessed using the Rotarod and Photobeam Activity System, respectively, at both 72 hours and 14 days. Sustained BBB permeability was also investigated in this cohort using the same dye used in the acute phase cohort. We saw significant BBB permeability at 24 hours post-TBI time point, but our analysis at day 16 post-TBI is still ongoing. The Rotarod test showed no significant effect on vestibulomotor function at 72 hours or 14 days. Injured rats showed significant deficits in speed and rearing time and a significant increase in resting time compared to sham at 72 hours. At 14 days, injured rats showed significantly increased speed over shams. These results indicate that the Maryland Model of TBI produces significant acute vascular leakage at 3 days and spontaneous motor deficits at days 3 and 14 post-TBI. This model requires further validation through the characterization of cognitive and memory deficits.

# ABSTRACT

## Interaction of 14-3-3 $\zeta$ and UCH-L1 with $\alpha$ -S in Parkinson's Disease

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Sponsored by: Robert Amato, DO, Department of Internal Medicine – Oncology; Reynolds Brobey, PhD, IMM Center for Proteomics and Systems Biology

Supported by: Robert Amato, DO, Department of Oncology, The University of Texas at Houston Medical School – Office of the Dean

Key Words: Parkinson's Disease, GST-14-3-3 $\zeta$ , UCH-L1, Antibodies, Immunoprecipitation

**Introduction:** Overproduction and aggregation of the protein alpha-synuclein ( $\alpha$ -S) has been shown to create lewy bodies in humans, suggesting that the protein plays a role in causing Parkinson's disease. Normally,  $\alpha$ -S helps form pre-synaptic vesicles for neurotransmitters, but the destruction of its normal tetramer form helps cause oligomerization and aggregation. The presence of a (thus far) unknown protein co-purified with the protein GST-14-3-3 $\zeta$  has been shown to curb the oligomerization process and aggregation of  $\alpha$ -S by keeping it in its natural form (Brobey et al, unpublished data). To better understand the role and capabilities of 14-3-3 $\zeta$  proteins in the human brain, researchers have tried to understand its various interactions with other proteins. Here, we decided to test whether UCH-L1, an ubiquitin proteasome hydrolase protein known to play a role in the onset of Parkinson's disease, directly interacts with  $\alpha$ -S /14-3-3 $\zeta$ .

**Methods:** To assess this, we used mouse monoclonal antibodies, conjugated to agarose beads, against the HA-peptide. The antibodies serve as bait for HA-ubiquitin-aldehyde, a known inhibitor of UCH-L1. Our hypothesis is that UCH-L1 forms complexes with GST-14-3-3 $\zeta$  to inhibit alpha-synuclein oligomerization. The HA is a sequence of 9 amino acids imbedded in the original ubiquitin-aldehyde protein sequence. Since ubiquitin-aldehyde theoretically binds to UCH-L1 in order to inhibit it, we reasoned that by immunoprecipitating the HA-ubiquitin-aldehyde/GST-14-3-3 $\zeta$  complexes with the beads, UCH-L1 will theoretically also precipitate out. Furthermore, if GST-14-3-3 $\zeta$  indeed interacts with UCH-L1, GST-14-3-3 $\zeta$  should also be present in the precipitate. We incubated specific amounts of antibodies (with beads), HA-ubiquitin aldehyde, GST-14-3-3 $\zeta$ , and  $\alpha$ -S (or not) in a buffer of PBS supplemented with protease and phosphatase inhibitors. Incubation was done overnight at 4°C on a rotating wheel. The beads were then precipitated by centrifugation, washed three times, and boiled for 5-10 minutes with SDS loading buffer. Eluted bead-bound proteins were then analyzed via SDS-PAGE and Western blot. Proteins separated on the SDS-PAGE were excised for mass spectrometry (MS) analyses; a replicate gel was Western-transferred onto a Polyvinylidene fluoride (PVDF) membrane and probed with anti-UCH-L1 antibody to reveal the presence of the protein. While we did see the expected ~26 kDa signal, other cross-reactive bands were also present. The results from the MS are pending; the presence of UCH-L1 will suggest that the protein does indeed interact with GST-14-3-3 $\zeta$  and may contribute to the inhibition of alpha-synuclein oligomerization (or at least with another protein in the GST-14-3-3 $\zeta$  complex).

## ABSTRACT

### Molecular Epidemiology of *Clostridium difficile* Infection at a University Hospital in Houston

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Sponsored by: Herbert L. DuPont, M.D., Director, Center for Infectious Diseases, University of Texas-Houston School of Public Health

Supported by: Zhi-Dong Jiang, M.D., DrPH, School of Public Health

Key Words: *Clostridium difficile*, hospital, environment, epidemiology

**Objective:** *Clostridium difficile* infection (CDI) is the most common healthcare infection in the U.S. The environment is presumed to be the source of hospital-acquired CDI. The purposes of this study were to evaluate the occurrence of hospital contamination by *C. difficile* and to look for hospital acquisition of CDI using molecular typing of strains to look for strain clustering.

**Methodology:** During a 7 1/2 month period, patients admitted with CDI infections and their rooms were routinely sampled for *C. difficile*. The patient rooms/bathrooms and an adjacent control room were sampled once a week for 3 weeks. Samples were streaked onto a *Clostridium difficile* agar plate and PCR was performed on the isolates to confirm the presence of *C. difficile*. If the isolate was identified as *C. difficile*, it was ribotyped to allow cluster analysis by performing similarity dendrograms.

**Results:** 145 *C. difficile* strains were isolated and categorized into 5 ribotype clusters with 2 out of the 5 clusters accounting 126/145 (87%) of the strains. Of 40 contaminated rooms, 17 (43%) showed homology between CDI patient strains and rooms strains with 2 of 29 (11%) of *C. difficile* from adjacent control rooms showing homology with the patient strain next door. The hypervirulent NAP1 strain was found in 26% of all isolates. The 5 outbreak clusters were documented throughout the study time period showing active disease transmission.

**Conclusion:** Nearly all *C. difficile* strains encountered in the study were part of clusters causing multiple cases of CDI with contamination of the environment. Two endemic strains were responsible for a majority of illness and will be targets of control programs. Spread of *C. difficile* was shown from patients to their rooms and to other rooms on their floor.

**Discussion:** Our data are consistent with studies in the literature on rates of room contamination and frequency of NAP1 strain. The unique aspects of this study are documentation of a limited number of strains in the hospital setting responsible for endemic and epidemic disease. The study will lead to efforts to control infections through infection control and room decontamination methods.

## ABSTRACT

### Designing and Constructing Trimethoprim Inducible System Vector for Controllable Expression of Neural Lineage Specific Genes

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Sponsored by: Ying Liu, MD, PhD, Department of Neurosurgery

Supported by: Ying Liu, MD, PhD, Department of Neurosurgery, Department of Neurosurgery and Bentsen stroke fund; The University of Texas at Houston Medical School - Office of the Dean

Key Words: Inducible system, dd, TMP, Olig2

Inducible systems are important tools for research on the developmental pathways or elucidating the underlying molecular mechanisms. Current inducible systems often target the DNA (Cre-Lox method), the transcription of DNA (Tetracycline-regulated transactivator), or at the RNA level (RNA interference). All these systems, however, require a delay period to degrade existing proteins due to the nature of the perturbation. A more direct and reversible method to rapidly target the protein of interest was developed by fusing a mutant of E. Coli dihydrofolate reductase (ecDHFR) to the gene of interest. The mutant ecDHFR, named destabilizing domain (dd), was engineered to degrade when expressed in cell without its ligand Trimethoprim (TMP), an inexpensive antibiotic. The fusion protein gained the instability conferred by ecDHFR and thus became regulated directly by TMP. Not only does the dd-TMP system overcome the experimental delay, it allows for a greater fine-tuning and temporal/spatial control not possible before. In addition, the ability of TMP to cross blood-brain barrier makes it ideal to study the central nervous system.

In this project, we attempted to take advantage of the dd-TMP system to study *Olig2* gene, a basic loop-helix-loop transcription factor that is important in the development of oligodendrocyte and has been implicated to play a role in Down syndrome. Using the Gibson Assembly method, we constructed a vector containing four fragments in sequence: *dd*, *Olig2*, *T2A* and *GFP*. We also constructed two other vectors using regular restriction digestion method: *dd-Olig2* and *dd-GFP*. Together these three vectors provide the useful molecular components to elucidate the role of *Olig2* in the development of oligodendrocyte and Down syndrome pathology.

# ABSTRACT

## Displaced Ganglion Cells in Primate Retina

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Sponsored by: David W. Marshak, PhD, Department of Neurobiology and Anatomy

Supported by: National Eye Institute Grant EY06472 - Structure and Function of Primate Retinal Neurons

Key Words: Primate, melanopsin, CART, neuropeptide

Cocaine- and amphetamine-regulated transcript (CART) peptides have been localized to neurons throughout the brain and have a variety of functions. In the mouse retina, CART has been found in dopaminergic amacrine cells. In the baboon retina, CART was localized to at least two morphological types of amacrine cells, which are homologous to A17 cells in other mammalian retinas. To determine whether the amacrine cells were GABAergic, frozen sections of baboon retina were labeled with antibodies against CART and GABA. In addition to finding that A17 amacrine cells were positive for both CART and GABA, we also found a small population of cells that were CART-positive but GABA-negative. These cells appeared, based on their morphology, to be ganglion cells that were displaced to the inner nuclear layer (INL). Two whole-mount preparations were then labeled with anti-CART antibody for morphological analysis of these displaced ganglion cells. However, using NeuroLucida neuron tracing software and Zen microscope software, it was not possible to reliably identify ganglion cells by their morphology alone. We then conducted a series of immunohistochemical double labeling experiments. Frozen sections were labeled with anti-CART and anti-RBPMS (RNA-binding protein with multiple splicing), a known marker for retinal ganglion cells. We predict that CART-positive displaced ganglion cells would be positive for RBMPS, whereas CART-positive amacrine cells would not. This would provide a reliable method of distinguishing between the two cell types. In addition, frozen and vibratome sections were labeled with anti-CART and either one of two antibodies directed against the photopigment melanopsin. Melanopsin is contained in intrinsically photosensitive retinal ganglion cells, which are involved in circadian entrainment and the pupillary light reflex. One population of these melanopsin-positive cells is known to be displaced to the INL, and these are the only type of ganglion cell regularly found there. Therefore, we predict that the CART-positive displaced ganglion cells also express melanopsin. Results from these double labeling experiments are expected in August.

## **ABSTRACT**

### **The Role of Human Polyomavirus Small T Antigens in Cutaneous Diseases**

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Sponsored by: Stephen K. Tyring, MD, PhD, MBA, Department of Dermatology

Supported by: Molecular Basis of Infectious Disease NIH sponsored training grant T32  
AI055449-07

Key Words: MCPyV, TSPyV, HPyV6, 4E-BP1 phosphorylation, PPM1G

Merkel cell polyomavirus (MCPyV), trichodysplasia spinulosa-associated polyomavirus (TSPyV), and human polyomavirus 6 (HPyV6) are implicated in the pathogenesis of Merkel cell carcinoma (MCC), the development of trichodysplasia spinulosa (TS), and the neoplastic growth of keratinocytes in response to BRAF inhibitors, respectively. Although the association of these polyomaviruses with cutaneous diseases is well-documented, their pathogenic roles remain to be further defined.

MCPyV, TSPyV, and HPyV6 viral genomes all encode small T (sT) antigens, which may regulate the phosphorylation status of proteins critical for signal transduction, such as eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Hyperphosphorylation of 4E-BP1 contributes to cell survival and proliferation. In the current study, we performed western blot analyses to determine 4E-BP1 phosphorylation in cells with inducible overexpression of MCPyV, TSPyV, and HPyV6 sT antigens. Our data showed that overexpression of these three polyomavirus small T antigens differentially regulated 4E-BP1 phosphorylation. Specifically, it was markedly enhanced by MCPyV sT; moderately elevated by TSPyV sT; and minimally upregulated by HPyV6 sT. These findings suggest that these three polyomaviruses have specific pathogenic mechanisms through different actions of their small T antigens.

To further understand the mechanisms of the above polyomavirus small T antigens, we performed co-immunoprecipitation and His-tag pull-down assays to determine whether protein phosphatase Mg<sup>2+</sup>/Mn<sup>2+</sup> dependent 1 G (PPM1G), a phosphatase that dephosphorylates 4E-BP1, is associated with MCPyV, TSPyV, and HPyV6 sT antigens. MCPyV sT presented the strongest PPM1G binding capacity; TSPyV sT displayed moderate affinity for PPM1G; and HPyV6 sT exhibited the lowest level of interaction with PPM1G. These observations suggest that the three small T antigens bind to PPM1G with distinct affinity and may inhibit its activity to different extents, leading to varying levels of 4E-BP1 phosphorylation.

In summary, our findings provide novel evidence for a distinct role of 4E-BP1 in the pathogenesis of polyomaviruses in different cutaneous diseases.

## **ABSTRACT**

### **The Generation of Plasmid Inserts using Assembly PCR**

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Sponsored by: Guangwei Du, Ph.D, Department of Integrative Biology and Pharmacology

Supported by: Guangwei Du, Ph.D, Department of Integrative Biology and Pharmacology;  
The University of Texas at Houston Medical School - Office of the Dean

Key Words: Plasmid, Assembly PCR, lipid signaling pathway

**Background:** Extracellular signaling from cytokines and other growth factors constitutes a large field of study in molecular biology. Activity of cytokines and growth factors leads to the activation of a complex lipid signaling network which controls important cellular processes. A major goal in biology is to better understand these lipid signaling pathways so that we may develop new therapeutic strategies for the treatment of diseases related to this pathway. However, a study of the lipid signaling pathway requires altering of the expression of genes in cells. This change in gene expression can be induced through the introduction of a plasmid carrying a gene for a lipid modifying enzyme. By observing the morphological and metabolic changes within the cell, it is possible to determine the function that the gene plays in the cell and thus better understand its role in the lipid signaling network. A method known as Assembly PCR will be used in order to generate the desired full length cDNA sequence that was originally cloned in two different plasmids. In these experiments, we sought to generate plasmids with the desired gene inserts to be used for future experimentation.

**Methods:** The plasmid inserts were generated by using four primers. Two of the primers were reverse complements to each other and the remaining two primers were designed to anneal to the terminal ends of the desired sequence and extend in the direction of desired gene. The complementary primers were designed so that the resulting products would have a 20-25 base pair overlap with each other. During the first round of PCR, two "fragments" of DNA were amplified. Each fragment was amplified using a terminal primer and one of the complementary primers. The second round of PCR involved using the two DNA fragments generated during the first round of PCR as a template and priming the replication of DNA with the two terminal primers. All PCR products were purified using gel purification and the Qiagen Gel Purification kit. The gene insert was subsequently ligated to a plasmid backbone and the plasmid was amplified through the transformation of competent E. Coli cells.

**Results:** A total of three gene inserts were generated using Assembly PCR. The identities of these gene inserts were confirmed through sequencing. The function of these genes will be confirmed through the transformation of mammalian cancer cells.

## ABSTRACT

### Structural Analysis of Oncogenic Mutant G12D and G13D of H-Ras: Implication for Function and Disease

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The University of Texas at Houston Medical School – Office of the Dean

Key Words: H-Ras, cancer, G12D, G13D, mutations

**INTRODUCTION:** The Ras superfamily proteins are essential for a variety of cellular functions, and can be divided into five subfamilies. All share the same molecular architecture and capacity to bind and hydrolyze GTP to execute their physiologic functions. In humans, three isoforms of the Ras subfamily are commonly expressed: H-Ras, N-Ras and K-Ras. Malfunction of these proteins due to somatic mutations is associated with about a quarter of all human tumors. Interestingly, even the same mutation at neighboring positions, such as G12D and G13D, on a particular Ras isoform can lead to different cellular outcomes. However, the precise mechanistic origin of these differences remains unclear. The goal of this project is to explore how the same glycine-to-aspartate substitution at positions 12 and 13 of H-Ras can differently affect structure or dynamics and thereby function. **METHODS:** We have compared the structures of wild type, G12D and G13D H-Ras proteins. The crystal structure of wild type H-Ras was obtained from the protein data bank (PDB, ID: 5P21). Structural ensembles for G12D and G13D were derived from multiple molecular dynamic (MD) simulations, which generated a total of 500ns-long trajectories for each system. The resulting structures (or movies) were loaded onto the visual molecular dynamics (VMD) program for alignment and visualization. Specific analyses performed in this study included measurements of hydrogen bonding propensities, root mean square deviations, root mean square fluctuations as well as inter-atomic distances. **RESULTS AND CONCLUSIONS:** The distribution of distances between the functionally critical residue tyrosine 32 side chain oxygen atom and the nucleotide gamma-phosphate was analyzed both in G12D and G13D. The results indicated a much wider distance distribution in G13D (3.5 to 17 angstroms) than in G12D (3.5 to 5 angstroms). Comparing snapshots at the GTP binding site over the entire simulation period showed that tyrosine 32 was pushed away from the nucleotide by aspartate 13 in G13D; there is a clear correlation between the movement of tyrosine 32 and aspartate 13 in G13D but not in G12D. Another measurement of distances between the gamma-phosphate and tyrosine 32 side chain oxygen on the one hand, and aspartate 13 side chain and sodium ions within 3.5 angstroms of the nucleotide on the other, further indicated that the nucleotide binding site of G13D—but not G12D—is accessible to solvent and stably binds a metal ion. This result suggests that the intrinsic and GAP-assisted catalytic activity of the two oncogenic proteins is likely different, which represents the first initial clue about the source of functional differences between these closely related mutant forms of H-Ras.



# ABSTRACT

## Role of Mitochondria in Craniofacial Development

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Sponsored by: Dr. Junichi Iwata, DDS, PhD, Assistant Professor, Department of Diagnostic & Biomedical Sciences, UTHealth School of Dentistry

Supported by: UTHealth School of Dentistry Research Office and Junichi Iwata, DDS, PhD, Assistant Professor, UTHealth School of Dentistry

Key Words: craniofacial development, mitochondria, fusion, fission

**Introduction:** Mitochondrion is the organelle that is responsible for ATP generation, signaling, differentiation, apoptosis, and growth of cells. Recent studies indicate that fusion and fission of mitochondria are vital for cellular homeostasis by exchanging and complementing contents of mitochondria, suggesting that they are crucial for embryogenesis. However, it is still largely unknown whether mitochondria fusion and fission contribute to craniofacial development.

**Objective:** The purpose of this project is to investigate a possible relationship between mitochondrial molecules and craniofacial development.

**Methods:** We searched for literatures related to mutations in mitochondria fusion (*OPA1*, *MFN2*, and *GDAP1*) and fission (*DRP1*, *LETM1*, and *DHODH*) molecules.

**Results:** We found that five human disorders are caused by the impairment of mitochondrial dynamics: Kjer's disease (mutations in *OPA1*), Charcot-Marie-Tooth neuropathy (mutations in *MFN2* or *GDAP1*), abnormal brain development (mutations in *DRP1*), Wolf-Hirschhorn syndrome (mutations in *LETM1*), and Miller syndrome (mutations in *DHODH*). For example, gene mutations in *LETM1* cause cleft lip and palate and skeletal anomalies in humans. Gene mutations in human *DHODH* result in severe micrognathia, cleft lip and palate, and coloboma of the eyelid.

**Conclusion:** Our study suggests that molecules involved in mitochondrial fusion and fission are vital for the formation of craniofacial structures. Future studies involving the detailed pathway analysis of the fusion and fission process would provide more insights into how these processes are responsible for craniofacial birth defects.



# International Medical Students

# ABSTRACT

## AHCC Modulates Hypertension in SHR Rats

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Class of 2017

Sponsored by: Marie-Francoise Doursout, PhD, Department of Anesthesiology

Keywords: AHCC, nitric oxide (NO), Hypertension

### Background:

Hypertension and cancer are the primary causes of mortality worldwide. Spontaneous hypertensive rats (SHR) are a genetic model of hypertension that is widely accepted in medical research because of the features they share with idiopathic hypertension in Humans. A large body of evidence indicates that patients with essential hypertension and/or cancer are characterized by endothelial dysfunction due to impaired nitric oxide (NO) availability secondary to oxidative stress production. Although conventional medicine has extensively been used to treat inflammation/oxidative stress in diseases such as hypertension and cancer, our proposed studies provide strong evidence that direct Active Hexose Correlated Compound (AHCC, Amino Up), produced from the mycelia of shiitake inhibit oxidative stress in hypertension. We hypothesize that AHCC could be an effective therapeutic intervention in diseases inducing endothelial dysfunction, e.g. hypertension, inflammation and/or cancer, especially when the nitric oxide signaling pathway is impaired.

### Methods:

Spontaneously Hypertensive (SHR; n=6) rats and their counterparts Wistar Kyoto (WKY; n=6) rats were surgically instrumented to continuously record Mean arterial blood pressure (MAP) and Heart rate (HR). Following recovery, animals were pretreated with LPS(20 mg/kg; IV) to induce inflammation in the presence and in the absence of AHCC in drinking water (10% for 3 days). MAP and HR were continuously recorded for 3 hours following LPS administration and/or AHCC. Simultaneously to hemodynamic measurements, blood samples were collected for Nitric oxide (NO) production using an ELISA assay. Animals were sacrificed at 3 hrs. and, gut and lung harvested to assess Wet to Dry (marker of edema formation) and histology using H&E staining.

### Result:

1. Our data show that AHCC decreased SHR-induced hypertension by 45 % whereas MAP remained unchanged in WKY control rats (Fig.1).
2. Furthermore, AHCC partially restored LPS-decrease in MAP in SHR rats. Heart rate remained unchanged (Fig 2-1, 2-2).
3. We are processing NO production data.

Figure 1

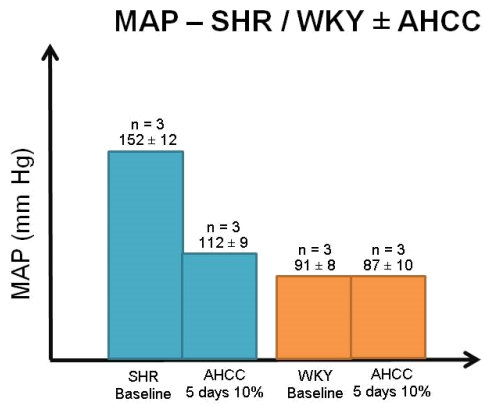


Figure 2-1

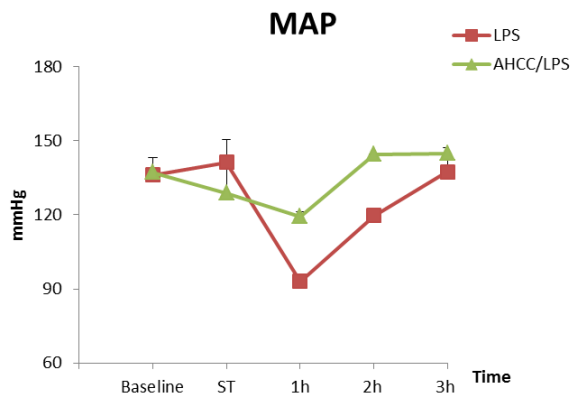
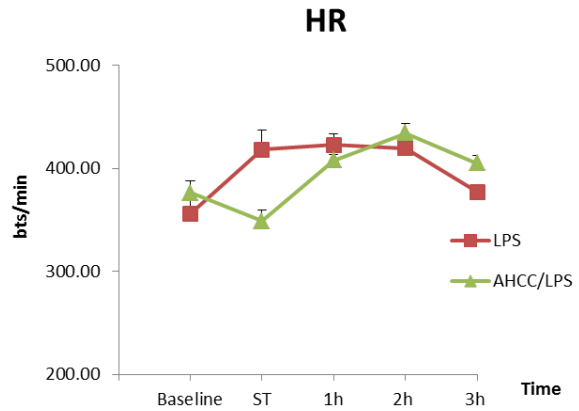


Figure 2-2



Conclusion:

Additional experiments are being conducted. In conclusion, our preliminary data demonstrate that AHCC might be an effective therapeutic agent in diseases inducing endothelial dysfunction, e.g. hypertension.

# ABSTRACT

## Over Expression of Reprogramming Factors on Glioma Cells

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Class of 2019

Sponsored by: Ying Liu, MD, PhD, Department of Neurosurgery

Keywords: Sox2; Oct4; glioma cells; proliferation; dedifferentiation

**Introduction :** Gliomas are the most common and aggressive type of central nervous system tumors, causing about 1.8 million deaths each year worldwide. Sox2 and Oct4 are two of the major reprogramming factors which convert somatic cells into the induced pluripotent stem cells (iPSCs). The purpose of this study is to investigate the effects of Sox2 and Oct4 overexpression on glioblastoma(GBM) cells and evaluate their proliferation and differentiation properties.

**Methods:** (1) Construction of inducible overexpression vectors in the Piggybac system (2) Three glioma cell lines, LN229、U87、U251 were transfected with a 2-in-1 Piggybac vector encoding Sox2 and Oct4. A GFP vector was used in the control groups. Cells were selected by G418, cultured in neural stem cell medium. qPCR of Sox2, Oct4 and neural stem cell genes was performed. MTT and cell migration assay were used to assess cell proliferation and migration behaviors.

**Results:** Glioma cell lines were successfully transfected by a 2-in-1 Piggybac vector encoding Sox2 and Oct4. Cells from three cell lines that overexpressed Sox2 and Oct4 were selected and isolated for subsequent characterization.

**Conclusions:** Overexpression of reprogramming factors Sox2 and Oct4 may alter the proliferation and metastatic behaviors of glioma cell lines.

# ABSTRACT

## The Effect of AHCC to Alleviate Inflammation

MIN HUANG

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Class of 2019

Sponsored by: Anil D. Kulkarni , M.Sc, PhD, Department of Surgery

Keywords: AHCC, LPS, Global Health

**Background:** The prevalence of overweight, obesity and diet related chronic degenerative diseases are regard as non-communicated diseases and have increased dramatically in many around the world. Diet habit is thought to be associated with the morbidity of NCDs, so the research on functional food or food extract is quite meaningful. The Active Hexose Correlated Compound (AHCC) an alpha-glucan rich nutritional supplement prepared extract from mycelium of mushrooms, which has been reported to be good for health for various physiological functions. This summer, I worked in the lab to find out if AHCC has any effect to alleviate inflammation.

**Method:** The experiment included 3 different groups of Spontaneously Hypertensive rats (SHR; n=6) and their counterparts Westar Kyoto rats (WKY; n=6). Group 1) AHCC alone group-10% AHCC (drink) for 3 days; Group 2) LPS alone group-to induce inflammatory response given water for 3 days and injected LPS (20mg/kg, i.v.); Group 3) LPS+AHCC group- given 10%AHCC (drink) and LPS. Use 'Powerlab' system to monitor the BP and HR of all the rats and take blood sample and tissues for further assay to measure the amount of nitrite and nitrate.

**Result:** MAP of the LPS group dropped sharply after injection while the MAP of AHCC+LPS group dropped slightly. And the data shows that AHCC decreased the hypertensive rats by 45 % of MAP while MAP remained unchanged in control group. AHCC repair the decrease in MAP in LPS group. Further research needs be continued in hypertensive SHR rats to understand mechanisms.

**Conclusion:** There is a difference in MAP between AHCC+LPS group and LPS group. The data shows that the decrease of MAP by LPS is repaired by AHCC and the heart rate remains unchanged. So AHCC may have the anti-inflammation effect. However, further experiments and data are needed to confirm our hypothesis.

In addition, I also wrote a short review on the current status of Chinese nutrition, food consumption and NCDs.

# ABSTRACT

## Delayed Paraplegia Following Thoracoabdominal Aneurysm Repair

KOHEI KANAMORI

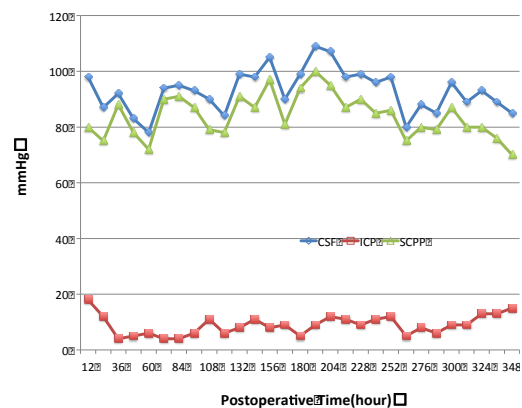
The University of Tokushima

Class of 2017

Sponsored by: Kristofer M. Charlton-Ouw, MD, FACS, Department of Cardiothoracic & Vascular Surgery

Keywords: Thoracoabdominal Aneurysm, TAAA, Paraplegia, COPS, CSF

Overall, 70% of the patients recover from Thoracoabdominal Aortic Aneurysm (TAAA) surgery without significant postoperative complications. Up to 30% of the patients develop some form of major complications, including renal failure, cardiac dysfunction, pulmonary failure, vessel ischemia, or neurologic deficits. For all of these complications, postoperative neurologic deficit has been the most devastating complications following TAAA repair. Postoperative neurologic deficit is mostly an ischemic injury, caused by the high CSF pressure. High CSF pressure compresses the spinal cord and eventually deteriorates the spinal cord perfusion (SCPP). Although lumbar drainage can protect the spinal cord intra-operatively, and can reduce immediate neurologic deficit, the spinal cord is still vulnerable during the early postoperative period (< 90days). Cerebrospinal drain status/Oxygen delivery/Patient Status (COPS) treatment has been established to significantly reduce the probability of this deficit. We experienced a patient who developed 4 paraplegias with this COPS protocol. As a past history, this patient had Hypertension, Gastritis, Acute Intestinal Obstruction, Hernia, Small Bowel Adhesions, Hyperlipidemia, and Synovial Cyst of Popliteal space. The patient was presented with extensive aortic aneurysm that was planned for resection and grafting in two separate hospitalizations. The stage I elephant trunk repair was completed. Three months later, stage II of the elephant truck procedure to repair the TAAA was initiated, and complicated by bowel perforation and enterocutaneous fistula. This patient was managed by gradual weaning of her lumbar drain to allow for gradual rise in her CSF pressure; thus avoiding paraplegia. We carefully monitored her SCF pressure, mean arterial pressure (MAP), spinal cord perfusion pressure (SCPP), and the Motor Power.



## ABSTRACT

### Evaluation of Rat Fracture Healing in a Model of Hormone Deficiency - Utility of Raman Imaging in Tracking Callus Maturation

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Class of 2016

Sponsored by: Catherine G Ambrose, PhD, Department of Orthopaedic Surgery

Keywords: Fracture healing, Raman spectroscopy,

**Introduction:** The evaluation of fracture healing has not changed significantly in the past few years. Recent publications have reported the utility of Raman in osteogenesis and other bone quality evaluating process. We therefore studied the correlation between Raman spectroscopy and micro-computed tomography (micro-CT) with the hypothesis that Raman spectroscopy can evaluate the bone quality during fracture healing equivalent to micro-CT.

**Methods:** Four Sprague Dawley rats divided equally into a bilaterally orchietomized group with low testosterone and a control group. Fractures were surgically induced at the middle third of one femur and were stabilized with K-wire pin fixation. One rat in each group was euthanized at 2 weeks and the other at 4 weeks. Quantitated images of micro CT were analyzed using GE MicroView and bone J to determine density of the callus and cortical bone in different positions. In addition, Embedded femurs are assessed using Raman micro-spectroscopy in the same positions. Raman maps acquired from callus and cortical bones are compared, and correlated with micro CT results. Pearson correlation analyses were used with  $p < 0.05$  considered significant.

**Results:** There were significant correlations between the average density and the mean values from both the Phosphate1/amide1 and FWHM data ( $p = 0.040$  and  $0.003$ , respectively). But the difference were not significant neither in the intact animals nor in the 4-week group alone. The average density were significantly correlated with FWHM data in the castrated group and the 2-week group ( $p = 0.046$  and  $< 0.000$ , respectively). The correlations were almost significant in callus bones but not cortical.

**Conclusions:** Raman imaging may be useful in tracking callus formation after fracture, spatially at early time points, for castrated animals, and when the "callus" type images are selected.



## ABSTRACT

### Polyethylene Glycol Hydrogels Functionalized with a Continuous Ile-Lys-Val-Ala-Val Concentration Gradient for Optimizing Neural Differentiation of Murine Embryonic Stem Cells in 2D

CHENG MA

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Class of 2016

Sponsored by: Laura Smith Callahan, Department of Neurosurgery

Keywords: Polyethylene glycol dimethacrylate, hydrogel, IKVAV, Murine embryonic cells

Spinal cord injuries (SCI) affect approximately 270,000 persons in the U.S. and cost the health care system over \$10 billion per year. Pluripotent stem cells which are capable at being differentiated into various cell types and are being studied as a treatment for SCI.

The aim of this study is to systematically identify the optimal concentration of IKVAV for the neuron differentiation of mESCs using a gradient approach.

50 mm × 10 mm × 1 mm hydrogel gradients were made with 12% 10kDa PEGDM with and without 1.9mM IKVAV. The hydrogels were made by two syringe pumps running in inverse linear ramping profiles from 0mL/h to 52mL/h over 75s into the mold and photo-polymerized with UV light (2.3mJ/cm<sup>2</sup>) for 6min. The gradient hydrogels were punched every 10 mm to make 6 discrete disc samples from each gradient. Every sample was evaluated for IKVAV concentration, swelling ratio and Young's Modulus. For the cell culture experiments, samples were seeded with mESCs and cultured for 6 days. Medium was changed every other day. The cell -seeded constructs were harvested at day 3 and 6 for analyses of gene expression, alkaline phosphatase and apoptotic activities. Statistical significance was determined using one-way or two-way ANOVA in conjunction with the Bonferroni post-test with a p-value of < 0.05.

Cells cultivated with IKVAV exhibited inferior ES-related mRNA expression and secreted a lower content of ALP suggesting that the cells were undergoing differentiation. TUJ1 mRNA expression, an immature neuron marker, increased under all of the conditions except for 920μM at day 3. The peak of the TUJ1 mRNA expression occurred in the 420 μM and 570 μM groups at day 6. Similarly, the highest mRNA expression of MAP2, a mature neuron marker, was detected in both 420 μM and 570 μM samples at day 6. A significantly longer neurite extension was identified in the cells cultured with 570 μM IKVAV. ESCs in the 920 μM group experienced a greater level of apoptosis than other test groups which may account for their compromised neural differentiation.

Based on the existing data, IKVAV concentrations between 420 μM and 570 μM provide for optimal neuron differentiation, while concentration of IKVAV at or above 920 μM cause apoptosis in mESCs.

# ABSTRACT

## Regulation of Ribosome Biogenesis by Sumoylation

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*Class of 2017*

Sponsored by: Catherine Denicourt, PhD, Department of Integrative Biology and Pharmacology

Keywords: Ribosome Biogenesis, Las1L, Pelp1, SUMO

Cells that divide rapidly, such as cancer cells, require an increase in their rate of protein synthesis to sustain the growth associated with fast proliferation. Because ribosomes are the main effectors of protein synthesis, their production is essential for cell division. Several oncogenes have been shown to regulate the synthesis of ribosomes and high rates of ribosome biogenesis are often observed in cancer cells. Thus, understanding how ribosome biogenesis is controlled at the molecular level could lead to the development of novel therapy for cancer. Emerging evidences from the Denicourt lab, as well as others, are suggesting that the small ubiquitin-related modifier (SUMO) system is an important player in the regulation of ribosome biogenesis. The goal of this project was to determine if Las1L and Pelp1, 2 proteins essential for ribosome biogenesis, bind to SUMO through SUMO interacting motifs (SIMs). We utilized the yeast two-hybrid system to evaluate if Las1L and Pelp1 interact with SUMO 1 and SUMO 3. Las1L and Pelp1 were cloned in fusion with the Gal4 DNA-binding domain and SUMO 1 and SUMO 3 in fusion with the Gal4 activation domain. Positive interactions we evaluated by measuring the activation of the B-galactosidase and HIS3 gene reporters. The preliminary analysis shows that Las1L interacts preferentially with SUMO 1, although weakly, and that Pelp1 interacts with both SUMO1 and SUMO3. Analysis of Las1L and Pelp1 sequences revealed that they contain putative SUMO-interacting motif (SIM) that could mediate these interactions. PCR mutagenesis was utilized to disrupt the putative SIM found on Las1L. Our future studies will consist in testing, using the two-hybrid system, if these mutations impair the binding of Las1L to SUMO.

## ABSTRACT

### GRK3 is Essential for Metastatic Cells and Promotes Prostate Tumor Progression

JIALIN SUN

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Class of 2015

Sponsored by: Wenliang Li, PhD, Assistant Professor, Division of Oncology, Department of Internal Medicine

Keywords: functional screens , essential kinases, GRK3,angiogenesis,metastasis

**Background:** Metastasis is responsible for over 90% of cancer deaths. However, biochemical and molecular mechanisms that regulate tumor progression to metastatic phenotype are still poorly understood, especially the control of survival and proliferation of metastatic cells. Kinases play key roles in regulation of many cellular processes.

Previously we employed an unbiased RNAi in vitro screen against human kinases and a focused cDNA in vivo screen to identify kinases that have novel roles in metastasis. From these, we discovered that G-protein-coupled receptor kinases 3 (GRK3) was one of the kinases that promote cancer progression.

**Experiments:** We carried out molecular and cell biology, biochemistry, in vitro and in vivo experiments to investigate the function and mechanism of GRK3 in cancer.

**Results & Discussion:** We found that GRK3 is essential for survival and proliferation of metastatic cells in culture and in mice. Moreover, it was also sufficient to promote primary prostate tumor growth and metastasis upon exogenous expression in poorly metastatic cells in mouse xenograft models. Mechanistically, we found that GRK3 functions, at least in part, through regulating several angiogenic factors and stimulating angiogenesis. Furthermore, GRK3 is overexpressed in human prostate cancers, especially in metastasis.

**Conclusion:** GRK3 plays an important role in prostate cancer progression and metastasis.

## ABSTRACT

### Characterization of Inducible BMPR2 Homozygous Knockout Mice

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Class of 2019

Sponsored by: Yanna Cao, MD, Tien C. Ko, MD, Department of Surgery

Keywords: Bone Morphogenetic Protein, Receptor, Cre-loxP

**Background/Significance.** Bone morphogenetic proteins (BMPs), members of the transforming growth factor  $\beta$  (TGF- $\beta$ ) superfamily, play crucial roles in cellular proliferation, differentiation, migration and apoptosis. BMPs transduce their signals upon binding to two different types of serine/threonine kinase receptors, type I (BMPR1) and type II (BMPR2). Previous studies have shown that heterozygous (BMPR2<sup>+/-</sup>) mice are phenotypically normal, whereas homozygous (BMPR2<sup>-/-</sup>) mice die at embryonic stage. Using Cre-loxP technology, we have generated inducible homozygous (Cre-BMPR2<sup>flox/flox</sup>) mice, which are alive and phenotypically normal. We hypothesize that BMPR2 gene expression is abolished in these mice upon Tamoxifen (TAM) injection for the induction of BMPR2 gene deletion.

**Methods.** To induce BMPR2 gene deletion, Cre-BMPR2<sup>flox/flox</sup> mice (n=5) were intraperitoneally injected with TAM (75 mg/kg body weight) for 5 days. Cre-BMPR2<sup>flox/flox</sup> mice (n=4) received corn oil as control. Seven days after completion of injections, the mice were euthanized, and the pancreas and liver tissue were harvested. For comparison of BMPR2 levels, the pancreas and liver samples were collected from heterozygous (BMPR2<sup>+/-</sup>, n=4) and wild-type (WT, BMPR2<sup>+/+</sup>, n=4) mice. Protein lysates were prepared and Western blotting analysis was used for detection of BMPR2 protein using 3 different primary antibodies against BMPR2.

**Results/Data.** Compared to WT mice, BMPR2 protein levels with the size of 115-130 kD in BMPR2<sup>+/-</sup> mice were significantly low (1- vs 0.48-fold in the pancreas, p<0.05; 1- vs 0.48-fold in the liver, p<0.05). Compared to corn oil-injected control Cre-BMPR2<sup>flox/flox</sup> mice, BMPR2 protein levels were lower (not significant) in the pancreas in TAM-injected Cre-BMPR2<sup>flox/flox</sup> mice with large variations (1- vs 0.42-fold, p>0.05), but significantly low in the liver (1- vs 0.10-fold, p<0.05).

**Conclusions.** BMPR2 gene deletion in BMPR2<sup>+/-</sup> mice results in 50% reduction of BMPR2 protein in the pancreas and liver, which is expected. Similarly, BMPR2 protein levels in TAM-injected Cre-BMPR2<sup>flox/flox</sup> mice were reduced in the pancreas and liver, although with large variations, which may be due to variations of TAM injection and absorption. As a future plan, we'll validate inducible BMPR2 gene deletion in Cre-BMPR2<sup>flox/flox</sup> mice at mRNA levels using quantitative polymerase chain reaction, and increase sample size. Since Cre-BMPR2<sup>flox/flox</sup> mice survive developmental stage, therefore, the adult mice can be used for further studies.