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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 1,900 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 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
Dean for Educational Programs
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Acknowledgements

This publication marks the completion of the twenty-sixth year of The University of Texas Medical School at Houston’s (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 Barbara J. Stoll M.D. and Patricia M. Butler, M.D., Vice 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 a short term research grant by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; 5 T32 DK007676).

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 McGovern Medical School at Houston or the Principle Investigator (PI).”
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## Medical Students

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Medical Students
ABSTRACT

Imaging CSF Outflow to the Lymphatic System in Swine Using Intrathecal Injection of Indocyanine Green

ALEXANDER BAREIS  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Sun Kuk Kwon, PhD, Eva Sevick-Muraca, PhD, Center for Molecular Imaging – Institute of Molecular Medicine

Supported by:  NASA, Translational Research Institute; Quantification of the lymphatic pump strength and its connection to the CSF

Key Words:  Lymphatic system, cerebrospinal fluid, indocyanine green, near-infrared fluorescence imaging, swine

Background:  Recent research has shown that the cerebrospinal fluid (CSF) and the peripheral lymphatic system are interconnected. Currently, the only modality for visualizing the connection between CSF and the lymphatic system is to perform injections into the cisterna magna, which is invasive to humans. Intrathecal injections are made into the subarachnoid space in the spinal canal and offer non-invasive access to the CSF. To our knowledge, intrathecal injection of indocyanine green (ICG) for imaging CSF outflow into the lymphatics has never been performed.

Objectives:  We seek to assess if intrathecal injection of ICG can be used to follow CSF outflow from the CNS into the cervical lymph nodes in the large animal model of swine.

Methods:  We conducted non-surgical intrathecal injection of ICG in swine using aseptic techniques. CSF was removed in equal volume to that of the ICG injected to maintain equilibrium regarding intracranial pressure. Near-infrared fluorescence imaging was performed to assess drainage of CSF from the CNS into the lymphatic system in vivo. Imaging occurred at injection lasting up to one hour post-injection. Lymph nodes, CSF, and components of the CNS were later excised and assessed for fluorescence.

Results:  We were unable to non-invasively detect CSF drainage to the cisterna magna or to the cervical lymph nodes in vivo due to depth beneath fat tissues, musculature, and spinous processes. However, we detected fluorescence around the coccygeal region in which less fat tissue was present. Excised lymph nodes and harvested CSF displayed marked fluorescence.

Conclusion:  CSF and lymph node fluorescence in our animal model suggest CSF outflow from the CNS into the lymphatic system, which was accomplished through non-invasive intrathecal ICG injection.
ABSTRACT

The Effects of Hurricanes on Preeclampsia and Fetal Loss

LISA BIRD

Sponsored by: James R. Langabeer, PhD, EdD, ACHE, MBA, Dept of Emergency Medicine
Supported by: Dr. Langabeer, Dept of Emergency Medicine
Key Words: Preeclampsia, hurricanes, disaster

The effects of man-made disasters such as nuclear radiation exposure on pregnancy has been studied extensively, but there is little objective information on the effects of natural disasters on pregnancy. Hurricanes frequently occur in the Atlantic Ocean during the period of June – November, posing a risk to large portions of the population. The majority of clinically relevant research has been performed only on hurricanes of historical significance, such as Hurricane Katrina, without inclusion of smaller, more typical hurricanes that patients are more likely to experience in the dataset. We sought to remedy this gap of knowledge, with a focus on preeclampsia and fetal loss outcomes. Preeclampsia remains a leading cause of maternal death in the United States, as well as a risk factor for stillbirth, but there is no test specific or sensitive enough to predict which patients will develop preeclampsia, so physicians rely solely on consideration of risk factors. We are performing multinomial logistic regression as secondary analysis on cohort data from the National Vital Statistics System collected by the U.S. Centers for Disease Control and Prevention to examine preclampsia incidence and fetal loss outcomes in counties affected by tropical hurricanes, with comparison of outcomes of similar months in examined counties during non-hurricane years. We selected vital statistics data from all U.S. states during years 1995 – 2005. Our models will use multivariate statistical analysis to test the effect of tropical hurricanes on preeclampsia and decipher whether intervening maternal, pregnancy specific, period, or socioeconomic factors contribute to the effect of tropical events on pregnancy outcomes.
ABSTRACT

Analysis of Pediatric Gunshot Wounds in Houston, Texas: A Social Perspective

JOE W. BREWER JR. McGovern Medical School at UTHealth Class of 2020

Sponsored by: David I. Sandberg, M.D., Vivian L. Smith Department of Neurosurgery
Supported by: David I. Sandberg, M.D., Vivian L. Smith Department of Neurosurgery
Key Words: Social Analyses of Pediatric GSW in Houston, Tx

Author(s):
Joe W. Brewer Jr., BA
Charles S. Cox, MD
Stephen A Fletcher, DO
Manish N Shah, MD
Michelle Sandberg, MD
Marcia L. Kerr, RN
David I. Sandberg, MD

Introduction: Gunshot wounds (GSW) are a leading cause of injury and death in children. This study explored social factors contributing to these tragic events.

Methods: We reviewed medical records of GSW victims between ages 0 to 15 who presented to a Level 1 pediatric trauma center between 1999 and 2016. Social work and case manager notes were reviewed to obtain data about factors contributing to the event.

Results: 358 children with GSW were treated between 1999 and 2016. Patients ranged from 2.5 months to 15 years old (mean=10.8 years). 292 patients (81.6%) were male, and 66 (18.4%) were female. The most common anatomic location of injury was the head and/or neck (n=166;46.4%). 7.8% (n=28) died, 31.6% (n=113) survived with a new disability, and 58.1% (n=208) survived without disability. Disability outcome was unknown in 9 patients (2.5%). 38.3% of injuries (n=137) were caused by handguns, 25.1% (n=90) by BB guns, and 12.6% (n=45) by shotguns or rifles. The weapon utilized was unknown in 24.0% (n=86). Firearms were secured in locked gun safes in just 1.7% of cases (n=6). 39.9% (n=143) were unsecured, and this information was not available in 58.4% (n=209). 45.5% of incidents (n=163) were intentional; 17 of these (4.7%) were suicide attempts. 48.9% of incidents (n=175) were accidental, and intent was unknown in 5.6% (n=20). The majority (n=226) of incidents (63.1%) occurred in a family residence. An adult was supervising the victim in only 26.3% of cases (N=94). Criminal charges were filed in 36 cases (10.1%). 15 victims (4.2%) were placed in CPS custody. Only 12.0% of charts (N=43) mentioned gun safety education being provided to the family.

Conclusion: Many pediatric GSW can be prevented with more attention paid to securing firearms, increased community education efforts, and other safety measures.
ABSTRACT

Long-term Impact of Pancreatectomy for Benign Cystic Lesions.

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Sponsored by: William E. Fisher, Elkins Pancreas Center, Baylor College of Medicine
Supported by: William E. Fisher, Elkins Pancreas Center, Baylor College of Medicine
Key Words: Pancreatectomy, pancreatic cystic lesions, diabetes, surgical outcomes

Background: Cross-sectional imaging technology has improved pancreatic cyst identification. Due to the fear that these cysts may develop into cancerous lesions, many are referred for pancreatectomy. Understanding the long-term outcomes of pancreatectomy is important to consider when removing a benign lesion. Previous studies have been limited by a 5-year follow-up period. This study aimed to quantify the effects of nutritional status, quality of life (QOL), and gland function after pancreatectomy for benign cysts.

Methods: Patients ≥ 3 years post-pancreatectomy for benign cystic neoplasms were selected from a prospectively maintained database at a high-traffic pancreas center. Pancreatic endocrine and exocrine function were evaluated. A history of chronic pancreatitis or PNET were exclusionary. Participation was obtained through telephone contact. Nutritional status, as well as pre- and post-operative QOL, was assessed using a modified Subjective Global Assessment (SGA) and the Functional Assessment of Cancer Therapy (FACT-Hep) questionnaires.

Results: Of 99 eligible patients, 46 (47%) enrolled. Median follow-up was 7 (2-12) years. At follow-up, 23 (50%) patients were deemed well-nourished (SGA A) while 33 (48%) suffered from mild-moderate malnourishment (SGA B). 29 (63%) of patients completed pre- and postoperative QOL surveys. Post-pancreatectomy QOL scores increased by a mean of 40 points (95% CI 31 to 50, p<0.005). 6 (13%) of patients underwent pancreatic enzyme replacement. New-onset diabetes was present in 14 (35%) of patients. Median diagnosis time was 11 (1-24) months post-resection.

Conclusion: While pancreatectomy for benign cystic disease may improve QOL, malnutrition and pancreatic insufficiency are present in a large proportion of the population when prospectively followed for greater than 5 years.
ABSTRACT

Regulation of dendritic arborization of hippocampal neurons by TRPC4 channels

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Sponsored by: Michael Zhu; Department of Integrative Biology & Pharmacology
Supported by: Michael Zhu
Key Words: TRPC4, dendritic arborization, mGluRs, growth cones

The notion that dendritic growth is regulated by extracellular cues that allow targeted growth for synaptogenesis is well supported, but the underlying mechanisms and molecular details of the pathways involved to bring about the final outcome remain unclear. It is clear, however, that dendritic growth is highly dynamic, including not only extension but also retraction and branching as the dendrites look to form synapses with other neurons. The dendritic arbor is the term given to the morphologically dynamic collection of all of the dendrites of a neuron. Dendrites, like axons, often mediate both anterograde and retrograde membrane flow with the formation of distal membrane structures called growth cones that may affect the subsequent growth or retraction. As the major excitatory neurotransmitter, glutamate also exerts a role in the overall morphology of the dendritic arbor, and until recently this has only been investigated with regard to ionotropic glutamate receptors, such as NMDA and AMPA receptors. However, metabotropic glutamate receptors (mGluRs) are also widely expressed in neuronal dendrites and they likely play roles in dendritic arborization too. As one of the major Ca\textsuperscript{2+}-permeable channels activated downstream from mGluR stimulation that signals through both G\textsubscript{q/11} and G\textsubscript{i/o} proteins, transient receptor potential canonical (TRPC4) represents an excellent candidate for mediating the effect of mGluR activation. Indeed, either genetic ablation or overexpression of TRPC4 caused a decrease in neurotrophin-induced dendritic arborization of cultured hippocampal neurons. Here, we compared dendritic morphology and growth patterns in primary hippocampal neuron cultures prepared from wild type (WT) and TRPC4 knockout (TRPC4KO) mice. To allow time-lapse fluorescence imaging of dendritic growth in individual neurons, we transfected the neurons with membrane associated green fluorescent protein (GFP). The neurons were grown in an environmental chamber with controlled conditions (37°C, and 5% CO\textsubscript{2}) while time lapse fluorescence video images were taken with a confocal microscope. Growth cone sizes and branch lengths were analyzed frame by frame using Image J. Either in the absence or presence of 5 µM glutamate in the culture medium, the proportion of dendrites showing growth cones and the growth cone sizes did not differ significantly between WT and TRPC4KO neurons. However, the short-lived growth cones are more common in TRPC4KO than in WT neurons. Moreover, when compared to WT, TRPC4KO dendrites exhibited an overall decrease in growth rate in response to glutamate. In addition, while the WT dendrite grew continuously over a period of 6 hrs, TRPC4KO dendrites tended to halt after the initial growth period of about 2 hrs. Surprisingly, the application of NMDA receptor blocker, AP5, extended the growth of TRPC4KO dendrites beyond the 2 hr period but arrested the growth of WT dendrites at around 2 hrs. These results suggest that TRPC4 channels and NMDA receptors play distinct, yet interrelated, roles in dendritic arborization of hippocampal neurons responding to the common stimulus,
glutamate. Their combined activities allow precise control of pairing between dendrites and incoming axons, setting the stage for synaptogenesis.
ABSTRACT
Cold and Exercise Exposure Stimulates Lipolysis through Upregulation of Adipose-Derived VEGF-A via Activation of Sympathetic Nervous System (SNS)

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Sponsored by:  Kai Sun MD, PhD, Center for Metabolic and Degenerative Diseases, Institute of Molecular Medicine
Supported by:  NIH (R01DK109001), American Diabetes Association (1-17-JDF-068), Pilot Award from Center of Clinical and Translational Studies at University of Texas Health Science Center at Houston (CTSA UL1 TR000371)
Key Words:  Obesity, Angiogenesis, VEGF-A, Lipolysis, Browning

Obesity is a major risk factor for many epidemic diseases including type 2 diabetes and cardiovascular disease (CVD). During obesity development, vascularization by angiogenesis in adipose tissue cannot keep the pace with the rapid speed of fat mass expansion. This may further cause local hypoxia, fibrosis, macrophage accumulation and inflammation which ultimately lead to systemic insulin resistance, the hallmark of type 2 diabetes. Importantly, we recently found that overexpression of a key angiogenetic factor VEGF-A in transgenic mice dramatically improves the vascularization in the obese adipose tissue, which hence protects transgenic mice not only against high-fat diet (HFD)-induced obesity but also insulin resistance. To observe potential inducible effects on VEGF-A, we placed mice under cold and exercise conditions, known methods associated with weight loss. We observed a more multilocular appearance of white adipocytes and significant upregulation of UCP-1, confirming a browning effect on the subcutaneous white adipose tissue (sWAT). These browning effects include increased energy expenditure and metabolic improvement in dissipating excess energy as heat. Furthermore, we found a massive upregulation of VEGF-A stimulating angiogenesis. To potentially mimic the cold and exercise exposure conditions, we used a doxycycline (Dox) inducible adipose tissue specific VEGF-A overexpression mouse model. In these transgenic mice we found that local overexpression of VEGF-A stimulates lipolysis in adipose tissue by upregulating hormone sensitive lipase (HSL) expression and enhancing its phosphorylation levels in adipocytes. As the result, the VEGF-A transgenic mice exhibited smaller adipocytes and reduced total fat mass shortly after VEGF-A induction. Intriguingly, the local norepinephrine (NE) levels in adipose tissue were dramatically increased in the transgenic mice. Immunofluorescent staining (IF) with anti-tyrosine hydroxylase (TH) antibody further showed higher density of neurons innervated in the adipose tissue of the transgenic mice. These findings clearly demonstrate that the sympathetic tone activated by VEGF-A plays a key role in adipose tissue lipolysis, which eventually leads to enhanced energy expenditure. These studies show that cold and exercise conditions stimulating the upregulation of VEGF-A may be potential targets for treating obesity.
ABSTRACT

A High-Kras Model of Ductal-Derived Pancreatic Adenocarcinoma and Cholangiocarcinoma

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Sponsored by: Jennifer Bailey, PhD, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases Grant, 5T35 DK 7676-24

Key Words: Pancreatic ductal adenocarcinoma, G12V Kras mutation, cholangiocarcinoma

Background and Hypothesis: Chronic inflammation associated with progressive pancreatitis increases the risk of pancreatic ductal adenocarcinoma (PDAC) by 13-fold. PDAC is an extremely deleterious malignancy and is the fourth leading cause of cancer-related mortality; despite an increase in knowledge regarding the pathogenesis, diagnosis, and management of PDAC, there still exists a substantial gap in understanding of its exact tumor biology and progression from chronic pancreatitis in some cases. Greater than 90% of patients with PDAC express activating mutations in Kras; recent literature have revealed that pancreatic acinar cells show greater neoplastic transformative potential than ductal cells in response to Kras mutations, and a two-hit model of PDAC has been described entailing either an additional tumor suppressor loss (TP53, SMAD4, CDKN) or chronic inflammation in conjunction with Kras mutations. In addition, a novel role for a high Kras G12V mutation to produce PDAC from acinar cells was recently studied in a murine model. This led us to hypothesize whether this G12V Kras mutation would transform ductal cells to PDAC and if so, propose a mechanism and therapeutic treatment.

Methods: Expression of an inducible KrasG12V allele (KrasG12V) in Hnf1b:CreER T2 (ductal cell specific) mice was performed using Tamoxifen to induce recombination after 6-8 weeks of normal growth. Mice were sacrificed at numerous timepoints, including day 5, day 7, and time of death, and their pancreatic and liver tissues were fixed, paraffin-embedded, sliced, and analyzed via immunohistochemistry (IHC). Confirmation of high-Kras activity was performed by western blot, and immunofluorescence (IF) analysis confirmed recombination. Several mice were treated with Bay 11-7085, a known NFkB inhibitor, and analyzed in the same manner at equivalent time points.

Results: KrasG12V mutations in the ductal cells of these mice resulted in not only rapid development of PDAC but also cholangiocarcinoma, with an average mortality at 10-12 days post-recombination. Histological analysis showed a significant increase in the ratio of abnormal papillary projecting cells to normal ductal epithelium from day 5 to time of death in both the pancreatic ducts and bile ducts. Furthermore, stellate-cell induced desmoplasia was significantly intensified in the pancreas, indicated by IF staining of smooth muscle actin (SMA). This rapid development of cancer likely involved upregulation of NFkB expression, confirmed with IHC in both endpoint pancreatic and liver slices. Treatment with Bay 11-7085 ameliorated not only the rapid development of PDAC and cholangiocarcinoma but also the desmoplastic
reaction, shown by reduced IF of SMA. Future studies of RNA transcriptome analysis and macrophage populations will reveal further insights into the development of PDAC.
ABSTRACT

The Trends of Clinical Biomarkers in Treatment Related Neuroendocrine Prostate Carcinoma

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Sponsored by: Robert J. Amato, DO, Department of Internal Medicine, Division of Oncology
Supported by: Robert J. Amato, DO, Department of Internal Medicine, Division of Oncology; McGovern Medical School at UTHealth-Office of the Dean
Key Words: Treatment Related Neuroendocrine Prostate Carcinoma, biomarkers

Introduction: Treatment related neuroendocrine prostate carcinoma is thought to develop due to resistance to androgen deprivation therapy and is associated with a poor prognosis in patients with metastatic prostate cancer. Patients with neuroendocrine prostate carcinoma present with low prostate specific antigen (PSA), bone and visceral metastases, prostate enlargement, and resistance to therapy. Cases of neuroendocrine prostate carcinoma often go under-diagnosed in the clinic due to a dearth of reliable biomarkers. However, increasing Neuron Specific Enolase (NSE) and chromogranin A levels have shown to correlate with androgen resistance, disease progression, and Gleason score. We performed a retrospective study to identify patients who developed neuroendocrine differentiation and followed chart biomarker trends over time.

Methods: Patients with prostate adenocarcinoma undergoing androgen deprivation therapy with Zytiga and Xtandi who developed metastatic castration resistant prostate cancer were selected for the study. Bone scans, CT scans, and MRI studies that were a part of the clinical assessment were analyzed. Results of blood obtained from 4-12 weeks during treatment procedures were assessed for the following markers: PSA, NSE, Chromogranin A, CEA, Testosterone, DH-T, Prolactin, PTH, Sedimentation Rate, C-reactive Protein, and Alkaline Phosphatase. This study was randomized and double-blinded.

Results: From the cohort of 58 patients, 9 patients showed low, baseline levels of PSA (< 20 ng/mL) with increasing levels of NSE and chromogranin A after Xtandi or Zytiga treatment. Five of the nine patients (55%) presented with progression of bony metastases from the most recent lab measurement. The mortality rate of the patients with neuroendocrine-type patterning was (44%).

Conclusion: Several patients in this study presented with slight increases in NSE and significant increases in Chromogranin A with baseline levels of PSA. About 55% demonstrated resistance to androgen deprivation therapy which may signify transition to neuroendocrine cell prostate carcinoma and progression of metastases. Biopsy results, Gleason scores, and an expanded profile of treatment are needed to confirm patients with neuroendocrine prostate carcinoma. These biomarkers remain of interest as clinical markers and are currently being further investigated.
ABSTRACT
The Impact of Enhanced Communication and Empowerment in Patient and Family Centered Care

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Sponsored by: Olakunle Idowu, MD, Department of Anesthesiology at MD Anderson Cancer Center

Supported by: The Society of Critical Care Medicine PCOR ICU Collaborative

Key Words: Improvements to patient and family centered care.

Learning Objectives:
The University of Texas MD Anderson Cancer Center participated in the Patient-Centered Outcomes Research (PCOR) ICU Collaborative through the Society of Critical Care Medicine. For this collaborative, we created the ICU Communication and Empowerment Project (ICE) to introduce a series of initiatives to promote family involvement in patient care while being sensitive to their values, cultural beliefs, and emotional well-being.

Methods:
A multidisciplinary team was created for facilitating information dissemination and implementing initiatives. Through our workgroup we instituted a visitor pass system, open visitation, and revamped the use of our two-way communication boards. We enhanced our waiting room experience by hosting ICU family centered events. Baseline (B) and Post Intervention (PI) family and clinician surveys were collected in the Rush University RedCap database.

Results:
There were 134 (B=79, PI=55) families and 127 (B=75, PI=52) clinicians participating in the surveys. The “good to excellent” average responses for family communications with ICU physicians and staff were B= 89.4% and PI=88%. The “good to excellent” average responses for family care and concern by ICU staff were B=90.9% and PI= 89%. Clinicians “strongly agree to somewhat agree” that having open visitation was beneficial for families (PI=64.3%). About half (50.9%) of the clinicians “strongly agree to somewhat agree” that communication with family members improved since the new two-way communication boards were implemented in the ICU.

Conclusion:
The SCCM PCOR Collaborative provided a platform for implementation of the ICE Project and effectively promoted patient and family centered care. Post intervention surveys showed that families remained happy with their ICU experience; however, the additional initiatives did not improve satisfaction significantly. This could be explained by an already high baseline interaction between families and our ICU staff, and/or inconsistent exposure to all interventions. Further work is needed to make these initiatives universally accessible in our practice.
ABSTRACT

Analysis of RSK Activity Following Serotonin Treatment

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Sponsored by: John H. Byrne, Ph.D., Department of Neurobiology and Anatomy
Supported by: John H. Byrne, Ph.D., Department of Neurobiology and Anatomy
Key Words: P90 ribosomal s6 kinase, Aplysia, Long-Term Facilitation

Background: The induction of long-term synaptic facilitation (LTF) in the mollusk Aplysia involves multiple signaling pathways, resulting in increased transcription of the CCAAT/enhancer-binding protein (C/EBP) gene, which is required for LTF. It has been proposed that the p90 ribosomal s6 kinase (RSK) phosphorylates and activates cyclic-AMP response element binding protein 1 (CREB1), thus promoting C/EBP expression and LTF. In humans, mutation of the RSK2 gene leads to Coffin-Lowry syndrome (CLS), resulting in cognitive deficits. My project aimed to validate a mammalian antibody to Aplysia phosphorylated RSK (pRSK), and subsequently use this antibody to measure pRSK levels at different time points post-treatment of serotonin (5-HT).

Methods: To validate the specificity of the mammalian antibody to Aplysia pRSK, protein lysates from Aplysia pleural-pedal ganglia were used for a Western blot, with dilutions of 1:500 for the primary antibody and 1:1000 for the secondary antibody in 5% dry nonfat milk. To determine whether the antibody is specific to phosphorylated RSK, a lambda phosphatase, applied at a concentration of 800 units, was used to pretreat lysate before antibody labeling to dephosphorylate pRSK. Following antibody validation, cultured Aplysia sensory neurons were either treated with five 5-minute 5-HT pulses to induce LTF, or with a vehicle solution. Neurons were fixed for immunostaining immediately post-treatment, or following 1, 5, or 24 hours post treatment. Cells were then incubated in 1:200 dilutions of pRSK primary antibody, followed by 1:200 dilutions of secondary antibodies. Immunofluorescence was then measured using a 63x Zeiss Confocal Microscope.

Results: Western blot analysis showed a single band around 90 kDa, which is the predicted molecular weight of pRSK. Also, no band was seen where pre-treated with the lambda phosphatase, thus confirming the specificity of the antibody to pRSK. Immunofluorescence analysis compared pRSK levels of 5-HT treated neurons normalized to the control group, fixed at the four previously mentioned time points, and suggested a delayed increase in pRSK after 5-HT (mean percentage control, ± SEM: 0 h, -0.17 ± 7.76%, n = 6; 1 h, -3.90 ± 3.60%, n = 2; 5 h, +24.81 ± 23.49%, n = 2; 24 h, +5.13 ± 7.29%, n = 4). However, a one-way ANOVA failed to show significance, possibly due to the small sample size. Further experiments will be needed to obtain a more accurate representation of the pRSK time course.
ABSTRACT

Changes in Retreatment Rates of Cerebral Aneurysms Over a 10-Year Period in a Population-Level Cohort

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Sponsored by: Sunil A. Sheth, MD, Department of Neurology
Supported by: University of Texas Rising STARs Award (PI: Sunil A. Sheth)
Key Words: Aneurysm, Endovascular treatment, Retreatment

Introduction: Prior studies have reported higher retreatment rates (RR) for cerebral aneurysms (CAs) after endovascular coiling (EC) compared to surgical clipping (SC). However, RRs have largely been derived from studies in the early 2000s and may not represent current practice.

Methods: Using administrative data on all discharges from acute care hospitals in California (2005-2011) and Florida (2005-2014), we identified patients with ruptured and unruptured CAs who were treated with EC or SC. Retreatments within 3 months were excluded, to minimize the inclusion of planned retreatments. Logistic regression was used to assess factors associated with retreatment, and results are presented as OR [95% CI].

Results: Among 19,650 patients with CAs, 12,441 (63.3%) were treated with EC and 7,209 (36.7%) with SC. Mean age was 57 ± 13, 72% were female and 12% were black. Between 2005 and 2014, the use of EC increased relative to SC (50% vs. 81%, p<0.0001). Retreatment occurred in 1488 (7.6%) patients (10.1% vs. 3.2%, EC vs. SC), with 89% within 2 years of index treatment. Retreatment was associated with age > 80 (OR 0.3 [0.2-0.5]), female sex (OR 1.6 [1.4-1.9]), black vs. white race (OR 0.8 [0.7-0.9]) and EC vs. SC (OR 3.5 [3.1-4.1]). Adjusted two-year RR decreased from 2005 to 2011 for patients with unruptured CAs treated with EC (8.7% vs. 6.8%, OR 0.95 [0.90-1.00] and Figure). Adjusted RR was unchanged for SC (mean RR 3.6% and 2.7%, unruptured and ruptured) and ruptured CAs treated with EC (mean RR 9.9%).

Conclusions: Analysis of two-year RR of CAs in a large real-world cohort demonstrates a continuous reduction in RR for unruptured CAs treated with EC in the last decade. These findings may reflect improving obliteration rates of EC for unruptured CAs.
ABSTRACT

Two Sides of the Same Coin: Features of Oncometabolism Exposed in the Stressed Heart

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Sponsored by: Heinrich Taegtmeyer, MD, DPhil, Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases (2T35 DK007676-24)
Key Words: Warburg Effect, PKM2, lactate, heart muscle

Background: In 1924, Otto Warburg reported that cancer cells fermented glucose into lactate even when oxygen levels were sufficient for mitochondrial respiration. Although a definitive explanation of the Warburg effect has remained elusive, one hypothesis proposes that the Warburg effect results in the accumulation of glycolytic intermediaries that are then shifted towards biosynthetic pathways that sustain rapid cellular growth. Like cancer cells, cardiomyocytes also modify their metabolism in response to stress. When stressed, the heart remodels and reverts to the fetal gene program, which results in an increase in the expression of the fetal pyruvate kinase isoform (PKM2), which has decreased activity compared to the adult M1 isozyme and increases lactate production. The lab recently found footprints of the Warburg effect in failing heart muscle, including an increase in expression of PKM2. Whether these glucose-derived products support cardiac hypertrophy remains to be determined.

Hypothesis: Glucose metabolism provides the biosynthetic precursors for cardiomyocyte hypertrophy induced by B-adrenergic agents via the Warburg effect.

Methods: Adult mouse ventricular myocytes (AMVMs) were plated in RPMI supplemented with glucose (11mM), insulin, 0.4 mM oleate and 2% bovine serum albumin and supplemented with isoproterenol or phosphate buffered saline. These conditions were maintained for 48 hours. Cells were harvested and protein extracted for immunoblotting of PKM2 and coupled enzymatic assay for determination of intracellular G6P and extracellular lactate. To identify the fate of glucose-derived carbons, a pulse-chase experiment was performed and AMVMs were plated with U-14C glucose. DNA, RNA, proteins, and polar and aqueous fractions were separated and extracted and DPMs of each fraction were determined.

Results: Treatment with isoproterenol results in AMVM hypertrophy when glucose is present in the medium. AMVMs treated with 3OMG, a glucose analogue (which can be transported into the cell but is not phosphorylated or metabolized), do not hypertrophy in response to isoproterenol. Treatment with isoproterenol and glucose results in a significant increase in the amount of lactate produced by AMVMs, compared to those AMVMs that were treated with glucose without isoproterenol. There was no increase in the amount of G6P produced between the two groups. There is significantly less 14C enrichment in the proteins of AMVMs treated with isoproterenol. There is no significant difference in 14C enrichment in any of the other macromolecules (DNA, RNA, polar and aqueous fractions). Immunoblotting for PKM1/2 in these conditions has been inconclusive.

Conclusions: My results suggest that while glucose is necessary for hypertrophy, it does not provide the building blocks. Therefore, in cardiomyocytes, the Warburg effect plays a different role than providing accumulation of biosynthetic precursors. I therefore propose that the
increase in aerobic glycolysis may provide the necessary chemical energy or reducing equivalents used to support the hypertrophic process in cardiac myocytes.
ABSTRACT

Dissecting Stress Granules in Osteosarcoma-associated Chemoresistance by LFS iPSC Disease Model

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Sponsored by: Dung-Fang Lee, Ph.D., Department of Integrative Biology and Pharmacology
Supported by: Dung-Fang Lee, Ph.D., Department of Integrative Biology and Pharmacology
Key Words: iPSC, Stress Granules, Chemoresistance, LFS, Osteosarcoma

The emergence of induced pluripotent stem cells (iPSCs) has created a reliable and potentially infinite model for studying disease mechanisms in vitro. The iPSC model was used to model Li-Fraumeni Syndrome (LFS) osteosarcoma, and demonstrated the ability to recapitulate the features of osteosarcoma, including gene signature and tumorigenesis. LFS is characterized by germ-line mutations of the TP53 gene leading to a variety of early onset tumors, such as adolescent osteosarcoma. In addition, mutations in p53 have been shown to confer chemoresistance. Recently, it was shown that the upregulation of stress granules (SGs) in some cancer cell lines confers chemoresistance. Therefore, we expected that there is an increase in SG formation in p53 mutated osteosarcoma leading to increased chemoresistance. Our aim was to determine if there is an upregulation of SG formation in LFS iPSC-derived osteoblasts.

To test our hypothesis, we first established our methods using cancer cell lines previously used in studying KRAS-mediated SG formation. We determined that cells would be treated with 100µM sodium arsenate for one hour, and then stained for GTPase activating protein (SH3 domain) binding protein 1 (G3BP) to detect SG formation. After staining, the cells were viewed using an immunofluorescence microscope and images of the cells were recorded. This methodology was applied to each series of experiments. Next, LFS patient and WT family member derived iPSCs were maintained, cultured, treated and stained. Additionally, osteosarcoma cell lines (p53 WT line O5A and U2OS and p53 mutated line HOS and 143B) were studied using the same methods. Finally, we used lentivirus-carrying different mutant p53 to modify cellular p53 status in osteosarcoma cell lines. Viral packaging plasmids and mutant p53 or WT p53/control plasmids were transfected into 293T cells in order to produce lentiviral practices to infect the WT p53 osteosarcoma cell lines O5A and U20S. The infected osteosarcoma cells were then treated and stained. The recorded images of all the stained cells were analyzed for the SG area inside the area of the cell, which is referred to as the SG index.

While our initial experiment proved our ability to induce SG formation and document the results, our results did not support our hypothesis. SG formation in LFS and WT iPSC derived osteoblasts showed SG formation that was not dependent on p53 mutation status. Only one of three mutated LFS derived osteoblast groups produced SG formation, while one of the two WT p53 osteoblast groups also produced SG. While both mutated p53 cell lines demonstrated stress granule formation, the WT p53 line, U2OS, showed the most SG formation. Finally, we ectopically expressed mutant p53 in WT p53 lines. Contrary to our expectation, there was no difference between cells ectopically expressing either mutated or WT p53. Thus, these findings do not support our original hypothesis that increased chemoresistance in LFS osteosarcoma is due to the formation of SGs. In summary, our results indicate SG formation is independent of mutated
p53 status, thus the differences in SG formation must be due to another unknown mechanism not studied in these experiments.
ABSTRACT

Association of perioperative opioid use and esophageal cancer recurrence: a retrospective study

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Sponsored by:  Dr. Juan Cata, MD, MD Anderson Department of Perioperative Medicine and Anesthesia
Supported by:  MD Anderson Department of Anesthesiology, Critical Care, & Pain Medicine
Key Words:  Anesthesiology, perioperative medicine, opioids, esophageal cancer

Background: Opioids are the most commonly prescribed analgesia in perioperative cancer care and pain management. However, recent experimental and clinical studies raise concern that differences in anesthetic regimens may play a role in oncological survival rates. Specifically, it has been suggested that use of opioids could modulate prognostic factors that impact cancer recurrence. The effects of intraoperative opioid use on esophageal cancer have only been addressed by a few reports. This study aims to investigate whether the use of opioid in the perioperative period plays a role on the incidence of recurrence-free survival and overall survival in patients with non-metastatic esophageal cancer.

Methods: We retrieved data on opioid on 773 patients with non-metastatic esophageal cancer who underwent surgery at the Texas MD Anderson Cancer Center. Patient data was grouped based on low or high levels of intraoperative morphine equivalent dosage (MEDD) (Recursive PARTitioning [rpart] cutoff = 710 MEDD). Kaplan-Meier analyses and Cox proportional analyses were conducted to assess the association between intraoperative morphine equivalent dosage (MEDD) on recurrence free survival (RFS) and overall survival (OS).

Results: Kaplan-Meier analyses indicated that lower MEDD (<710) was significantly associated with reduced recurrence-free survival (p = 0.0389) and marginally significant for poorer overall survival (p= 0.0784). With the adjustment of age, BMI, stage, histology, pre-operative chemotherapy, and post-operative chemotherapy, multivariate analysis indicated a significant association between the level of intraoperative MEDD (<710 vs. ≥710) and RFS (p-value=0.0165; HR=1.312, 95% CI: 1.051~1.638). Likewise, with the adjustment of age, BMI, stage, histology, preoperative chemotherapy, and postoperative chemotherapy, multivariate analysis indicated marginal significance in association between the level of intraoperative MEDD (<710 vs. ≥ 710) and OS (p-value=0.0994; HR=1.221, 95% CI: 0.963~1.547).

Conclusion: The results of this study indicate that the level of intraoperative opioids use may play a role in esophageal cancer recurrence and overall survival. However, we recognize that the retrospective nature of this clinical study may be influenced by confounding or unmeasured factors. Until randomized controlled studies explore this association further, opioids should continue to be a key component of balanced anesthesia in patients with esophageal cancer.
ABSTRACT
The Association of Adipocytokines with Insulin Resistance, Inflammation and Atherosclerosis in a Mexican-American Border Population

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Sponsored by: Absalon Gutierrez, MD, Division of Endocrinology, Diabetes, and Metabolism
Supported by: NIH NIDDK, 5T35DK007676-24

Key Words: Adipocytokines, cIMT, Diabetes Mellitus, Atherosclerosis, Mexican-American

Background: Leptin, resistin, and adiponectin are adipocytokines - hormones secreted from adipose tissue - which influence insulin resistance and atherosclerosis. Leptin increases energy expenditure and suppresses appetite. Resistin increases inflammation and vascular dysfunction. Adiponectin promotes anti-inflammatory mechanisms and whole body insulin sensitization. Mixed-population studies suggest that worsening insulin resistance is associated with higher levels of leptin and resistin, and with lower levels of adiponectin.

Significance: In Hispanic populations, the levels of three key adipocytokines - leptin, resistin and adiponectin - are unknown across various levels of insulin resistance. The relationship of these levels to carotid intima thickness (cIMT) - a marker of atherosclerosis - is also unknown.

Hypotheses: 1) In a Mexican-American population, increasing levels of leptin and resistin - as well as decreased levels of adiponectin - are associated with the increasing severity of insulin resistance and inflammation, 2) In a Mexican-American population, increased imaging evidence of atherosclerosis (via cIMT) is seen across rising levels of insulin resistance.

Experimental Design: Human subjects from the Cameron County Hispanic Cohort were studied via retrospective cross sectional analysis and stratified into three groups of insulin resistance (nondiabetic, prediabetic, and diabetes mellitus). The final study database only included subjects with measurements of aforementioned cytokines. Subjects were excluded based on age < 18 years old, tobacco use, pregnancy, active malignancy, major adverse cardiovascular events, and confounding medications (statins and relevant antihyperglycemic medications). There were 819 subjects (43%, 35% and 22% for nondiabetics, prediabetics and diabetics, respectively) for the study of adipocytokines and 249 subjects for the study of cIMT (34%, 50% and 16% for nondiabetics, prediabetics and diabetics, respectively).

Results/Data: Across the groups, univariable analysis (of log transformed values) showed significantly different levels of leptin (p<0.001), levels approaching significance for adiponectin (p=0.057), and no significant differences for resistin (p=0.1). After controlling for gender, hypertension, age, and BMI, adiponectin levels lowered significantly across increasing levels of insulin resistance (p=0.002) and resistin levels did not change significantly across groups (p=0.10). Compared to nondiabetics, leptin levels surprisingly decreased significantly among diabetics (p=0.013), while prediabetics had higher leptin levels than those among nondiabetics (p=0.011). cIMT levels heightened across intensifying insulin resistance (p=0.01).

Conclusion: In a Mexican-American population, diabetic subjects had lower levels of leptin compared to nondiabetics, which is contrary to our hypothesis. This argues for the presence of leptin deficiency, rather than the usual mechanism of leptin resistance, in this population of diabetic subjects. Also contrary to our hypothesis was the lack of change in resistin. As expected, adiponectin levels decreased across groups and cIMT measurement increased across groups.
These findings support more research on the role of leptin deficiency and diabetes in this population. The relationship of resistin to insulin resistance also merits further study.
ABSTRACT
Patient Reported Outcomes Following Sever Chest Injury

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Sponsored by: Dr. John Harvin, M.D., Charles E Wade, PhD
Supported by: McGovern Medical School Department of Surgery; CeTIR
Key Words: Sever chest injury, patient centered, patient reported

Introduction: Patient reported outcomes following injury are lacking. The National Institutes of Health and American College of Surgeons have called for the need to implement more patient centered methods in collecting post-discharge outcomes from large trauma registries.\(^1\) Chest injury is a common cause of mortality and morbidity.\(^{ii,iii,iv}\) We aim to better characterize short-term patient reported outcomes following severe chest injury.

Methods: After IRB approval, we conducted a prospective observational study from June 3, 2017 through August 5, 2017. Patients admitted to the Memorial Hermann Hospital-Texas Medical Center trauma services following blunt injury were screened for severe chest injury, defined as flail chest, $\geq 6$ consecutive rib fractures, or $\geq 1$ displaced rib fracture. Patients with spinal cord injury, preexisting cardiac/pulmonary disease, or bilateral LE non weight bearing fractures were excluded. In patients who consented, health status was assessed using the EuroQol-5D(5L) form and quality of life the standard gamble.

Results: Over the study period, 626 patients were screened and 42 patients met inclusion criteria. Twenty-two patients either did not consent or had an exclusion criteria, leaving 20 enrolled patients. The patients had a mean age of 45 years (SD 17) and were severely injured (mean Injury Severity Score 22 [SD 12]). The majority of rib fracture patterns included were $\geq 6$ consecutive rib fractures (14 or 70%), followed by $\geq 1$ displaced rib fracture (5 or 25%), and flail chest (1 or 5%). The mean EuroQol-5D(5L) visual analogue scale (overall health status) was 0.70 (SD 24); the mean visual analogue scale for patients in the United States is 80 (SD not known). The mean utility as measured by the standard gamble was 0.75 (SD 0.35). The EuroQOL-5D(5L) domains are shown below:

Conclusion: In this group of injured patients, severe chest injury resulted in a reduction of overall health status and quality of life. The domains with the lowest reported health status were usual activities and self care. This study is limited by unknown population norms for this group of patients. Future study will include a 6 month follow up to assess resolution of impaired health status and quality of life.
Mean Scores for EuroQOL-5D Domains

Score

Mobility Self-Care Usual Activities Pain Anxiety

0
ABSTRACT
Let the Right One In: High Admission Rate for Low Acuity Pediatric Burns

GRANT GARWOOD  McGovery Medical School at UTHealth  Class of 2020

Sponsored by: Kuojen Tsao MD, Pediatric Surgery
Supported by: Kuojen Tsao MD, Pediatric Surgery
Key Words: Pediatric Surgery, Burns


Introduction: More than 125,000 children present to Emergency Departments (ED) in the US every year, with less than 10% admitted for treatment. Many pediatric burns are minor and may be triaged in the Emergency Department (ED) with appropriate follow-up. The purpose of this study was to describe the status of emergency pediatric burn care triage to identify targets for value and quality improvement.

Methods: A retrospective record review of pediatric patients (<18 years) with primary burn injuries who presented to a tertiary, academic children’s emergency department in 2016 was conducted. Demographics, triage patterns, and injury characteristics such as total body surface area (TBSA) % burn were evaluated. Patients who were transferred to a burn specialty center for large burns (>30% TBSA) were excluded. Observation admission were those admitted to the hospital for less than 24 hours. Complications included graft failure, infection and ED revisit or readmission. Descriptive statistics, chi², and Wilcoxon rank sum tests were used for analysis. Multivariate logistic regression was used to evaluate the association of observation admission versus discharge from the ED.

Results: In 2016, 300 pediatric burn patients were triaged in the ED, with only 4 requiring transfer to a higher-level burn specialty center. Patients were typically young (median age 3.2 years, IQR 1.3-7.3), male (n=173, 58.5%), non-White Hispanic (n=135, 46.2%), and publically insured (n=226, 76.4%). The majority of patients were transferred from outside facilities (n=189, 63.9%) and arrived by ambulance (n=219, 74.2%). Scalding was the mechanism of injury for most children (n=166, 58.5%), followed by flame (n=49, 17.3%) and contact thermal injuries (n=46, 16.2%). Though most burns were small, not severe, and able to be debrided without sedation, the majority were admitted (n=235, 79.4%). In those admitted, length of stay was brief (median 1.5 days, IQR 1.9-3.9) with 36% admitted for less than 24 hours. There were few complications overall (n=12, 4.1%) and no difference in those admitted or discharged (p=0.27). Patient demographics, except for gender in patients admitted for less than 24 hours, were not associated with admission or discharge. Presentation after regular hours (07:00-19:00) but not day of the week, was associated with observation admission. After adjusting for gender, method of arrival,
transfer status, mechanism of injury, complexity, debridement requiring sedation, time
of presentation and TBSA, only arrival by
ambulance was associated with observation admission hours versus discharge from the
ED.
Conclusion: Though most burns were low acuity, the majority of children were
admitted. There may be an opportunity for improved resource utilization through
standardized admission criteria and discharge protocols.
ABSTRACT

Cross-talk between the gut and the brain in rats subjected to LPS-induced inflammation: Role of α-synuclein.

Gregory Gaskey  
McGovern Medical School at UTHealth  
Class of 2020

Sponsored by: Marie-Francoise Doursout, PhD, Department of Anesthesiology  
Supported by: McGovern Medical School at UTHealth – Office of the Dean, Marie-Francoise Doursout, PhD, Department of Anesthesiology  
Key Words: Parkinson’s, Gut-Brain-Axis, α-synuclein

Background: It is well established that the involvement of the gastrointestinal tract is of great interest as a contributing factor to the development and progression of neurodegenerative diseases. The dysregulation of the Gut-Brain-Axis (GBA) may be associated with gastrointestinal manifestations preceding disorders of cognitive and/or memory and learning process, supporting the hypothesis that the pathological process is spread from the gut to the brain. The extensive involvement of the gut in neurodegenerative diseases such as Parkinson’s disease, even in its early stages, has led to the evaluation of enteric α-synuclein as a possible biomarker. Therefore, the overall goal of the proposed study is to assess the time course of the compromised intestinal barrier capable of influencing brain function in rats challenged with LPS.

Hypothesis: Specifically, we hypothesize that alterations of the intestinal barrier (or leaky guts) enhances inflammation as well as the production of a unique protein α-synuclein which is characteristic of degenerative diseases.

Experimental Design: To induce inflammation, Lipopolysaccharide (LPS) was administered intravenously (IV) in rats at a dose of 20 mg/kg. A single dose LPS was elected based on previously reported results from a mouse model. Animals were divided into 2 groups (saline and 20 mg/kg LPS). Animals were also divided into 2 sub-groups (short term; 1 week and long term; 4 weeks). Following sacrifice at each time point tissues from the gut and brain (e.g. hippocampus and olfactory bulb) were harvested. We measured edema formation in the gut in rats subjected to LPS as compared to saline by wet/dry ratio. α-synuclein in the collected tissues was determined using ELISA (R&D Systems) at each time point. Protein concentration in each sample will be measured using a BCA protein assay kit. Data was analyzed by a one-way analysis of variance (ANOVA) to assess overall significance. When differences are significant, multiple within-comparisons were performed using Dunnett’s t-test. When changes are significant, the magnitude of changes in each experimental condition were compared using an unpaired t-test where p <0.05 was considered significant. Data is expressed as Mean ± SEM.

Results: Our data shows that LPS induced edema in the gut, suggesting inflammation. Although not yet finalized in the gut, our data demonstrates that increases in α-synuclein protein concentrations were time-dependent in the hippocampus.

Conclusion: We demonstrated that LPS challenge in rats induces edema in the gut. We also demonstrated increases in α-synuclein in the hippocampus in a time dependent manner. Currently, we are assessing increased α-synuclein in the olfactory bulb and gut to further understand the time course of deposition along the GBA and IL-6 in the plasma as an indicator...
of inflammation. We postulate that LPS induces an increase in α-synuclein concentrations in the gut and later spreads to the brain. Our ultimate goal is to reach an understanding between the gut and brain interactions to further locate effective therapeutic regimens to treat or prevent related neurodegenerative diseases.
ABSTRACT

Analysis of the Effects of Acute Blood Glucose Levels on Complications Incurred Following a Traumatic Injury in Patients with Diabetes Mellitus

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Sponsored by: Center for Translational Injury Research
Supported by: Dr. Charles E. Wade
Key Words: diabetes mellitus, trauma, HbA1c, complications, hyperglycemia

Introduction: Diabetes is a chronic disorder that affects more than 30 million Americans today. Approximately 25% of patients admitted to the hospital have diagnosed diabetes mellitus and nearly a third of patients with the disorder are undiagnosed. The prevalence of diabetes has incited extensive research that suggests patients with diabetes mellitus specifically are at an increased risk for traumatic injuries. Studies have shown that the disorder is associated with longer stays in the ICU, more days on ventilator support, higher rates of infections and other complications after trauma. However, other studies have shown that there are no differences between diabetic and nondiabetic trauma patients when comparing hospital length of stay, mortality, risk for deep infection or DVTs. We believe these conflicting results may be due to similarities between controlled diabetics and nondiabetics suggesting further analysis of the diabetic population is required. We hypothesized that patients who experience acute abnormal glucose levels, as indicated by random blood sugar and HbA1c levels upon hospital admission, will have an increased risk for complications and mortality.

Methods and Aims: We conducted a retrospective analysis of level I trauma patients admitted to the surgical trauma intensive care unit (STICU) at Memorial Hermann Hospital between the years 2011-2016. Patients were in the STICU for >7 days, >15 years old, non-obstetric and non-prisoners. Patients diagnosed with diabetes mellitus II prior to trauma were divided into two groups based on their HbA1c levels. Those with HbA1c < 6.5 were placed in the controlled diabetic group and those with HbA1c > 6.5 were placed in the uncontrolled diabetic group. Nondiabetic patients were divided into hyperglycemic (> 200 mg/dL) and euglycemic (< 200 mg/dL) groups. For continuous and count variables, we used the Kruskal Wallis test and the Pearson’s chi-squared test to assess associations between categorical variables. Poisson regression was used to assess the effect of diabetic category on complication rates after adjusting for injury severity score (ISS), age, race, ethnicity, trauma type, base excess, AIS-head and length of stay.

Results: During this study, 258 trauma patients were evaluated. Of the 83 diabetics, 51 had demographics, HbA1c and comorbidities recorded. 175 of the 175 nondiabetics had demographics, blood glucose and comorbidities recorded. Uncontrolled diabetics did not have a significant difference in complication rates when compared to controlled diabetic, nondiabetic hyperglycemic and nondiabetic euglycemic patients.

Conclusion: DM is a prevalent disorder among trauma patients and is associated with many complications. Uncontrolled diabetes has the potential to induce comorbidities. Further research is required to properly compare complication rates between diabetic groups.
ABSTRACT

Renal Presentation of Tuberous Sclerosis Complex

INA GROSE

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Sponsored by: Joshua Samuels, MD, MPH, Pediatric Nephrology and Hypertension

Supported by: Joshua Samuels, MD, MPH, Pediatric Nephrology and Hypertension

Key Words: Tuberous sclerosis, Afinitor (everolimus), Renal

BACKGROUND: Tuberous Sclerosis Complex (TSC) occurs in 1 out of 5,000-10,000 live births (1). TSC is an autosomal dominant disorder, presenting with loss-of-function mutations in TSC1 and/or TSC2 genes. The majority of individuals with TSC present with loss-of-function mutations in TSC1 and/or TSC2 genes. TSC1 encodes for the protein hamartin, expressed in most adult tissues. While the specific function is unknown, hamartin forms and stabilizes a complex with tuberin, the gene product of TSC2 (2). Tuberin is a protein that is ubiquitously expressed in all adult tissues. Tuberin contains a gene region that is homologous with the catalytic domain of Rap1GAP, a GTPase-activating protein that downregulates Rap1 protein. Rap1 acts as a GTPase to induce DNA synthesis (3). A loss of function mutation of tuberin leads to activation of Rap1, leading to elevated signaling for DNA synthesis and cell growth. The hamartin-tuberin complex inhibits cellular signaling mediated by the mechanistic target of rapamycin (mTOR). mTOR functions to regulate protein translation and cell cycle progression. In TSC, downstream modulators of mTOR, become unregulated, leading to unchecked tumor growth (2). The presentation of TSC is variable in age of symptomatic onset, tumor location, and tumor growth. The tumors that arise are benign hamartomas that present within the brain, skin, eyes, kidneys, and liver. Kidney lesions occur at a later onset but ultimately affect a majority (80%) of TSC patients (5). Renal manifestations of TSC most commonly present as angiomyolipomas (AMLs). Less commonly, benign cysts and renal cell carcinoma may occur. Progressive growth of AMLs within the kidney can lead to hemorrhage and interference with renal function, putting patients at risk for chronic kidney disease (6).

METHODS: We created a quality improvement-centered patient database highlighting the variable presentations of TSC to identify demographic and clinical variables that affect renal prognosis and management of TSC. Patient age, mutation phenotype, and renal lesion character were recorded to observe how these parameters affected renal lesion size and renal function. Additionally, the treatment of renal lesions, either with Afinitor (everolimus) or anti-hypertensives were recorded to determine if drug therapy led to improved prognosis of patients with TSC.

RESULTS: The established database included 256 total patients, where all patients who attended the TSC Center of Excellence in Houston, TX between September 2001 and July 2017 were eligible for consideration. Patients were predominately female (n=139, 54%), white (n=215, 84%) with 20% (n=52) of Hispanic identity. Although 43% of patients did not have genotyping done, TSC2 mutations were the most common genotype (n=102, 40%) followed by TSC 1 (9%) and no mutation identified (8%). Concerning TSC treatment, 40 (19%) of patients were given Afinitor and 32 (13%) of patients were given anti-hypertensive medications. Imaging procedures were performed on 124 patients, where MRI was the most common imaging modality (48%).
The renal imaging reports identified AML in 94 patients (37%), cysts in 109 patients (43%), followed by carcinoma (1%) and other lesions (8%). Based on the preliminary outcomes, the anticipated prevalence of TSC increases with an association with the female gender and increased age of symptomatic onset. Patients with TSC2 mutations will have a greater manifestation of lesions compared to other genotypes (7).

**Resources:**
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)’s Role in Autophagy

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

Supported by:  
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5T35DK007676-24

Key Words:  
PCSK9, atherosclerosis, autophagy

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a multifaceted protein best known for its role in degrading the low-density lipoprotein receptor (LDLR), making it a significant therapeutic target for atherosclerotic disease. A number of PCSK9 inhibitors have been released for patients whose cholesterol levels cannot be controlled on statins alone, however, PCSK9 has other complex interactions which remain to be elucidated. Previous work suggests that PCSK9 is involved in an autophagic process which regulates lipoprotein ApoB independently of the LDLR. PCSK9 also is found in the brain, where it is not fully understood, but is involved in a variety of processes such as neuronal apoptosis, stroke, and traumatic brain injury.

In order to further understand PCSK9’s role in liver and brain lipid metabolism and autophagy, previously generated siRNA, microRNAs (miRNAs) -601 and -632, and CRISPR/CAS9 RNA targeted against PCSK9 are to be transfected via the lipofectamine 2000 vector into HepG2 and U87 cells. At 48 hours post transfection the media is to be collected and cell lysate is to be extracted of protein and RNA. SDS/Page and subsequent western blotting will be performed on samples in order to observe relevant protein expression levels and qPCR will be run in order to quantify mRNA expression of PCSK9. We will examine LDL uptake in PCSK9 inhibited cells by incubating cells with fluorescent Di-LDL. Expected results are that PCSK9 will have lower expression which will lead to increased LDLR expression, decreased ApoB levels, and decreased low-density lipoprotein levels. In addition, novel observations of proteins involved in the autophagy pathway such as Akt, AMPK, ULK-1, Beclin-1, and Atg14L are expected in the liver and brain. Finishing this study will take future efforts to complete the data set. It holds high promise in further elucidating PCSK9’s role in autophagy and lipid metabolism both in the liver and brain. Understanding PCSK9’s mechanisms fully is critical to provide new therapeutic targets and give insight into potential side effects of its inhibition.
ABSTRACT

Exploring the family financial burden of outpatient pediatric surgical care and interest in telemedicine for post-operative care

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Sponsored by: Mary T. Austin, MD, MPH, Department of Pediatric Surgery  
Supported by: Mary T. Austin, MD, MPH, Department of Pediatric Surgery; McGovern Medical School – Office of the Dean

Key Words: telemedicine, pediatric surgery, clinic, cost

Introduction: Telemedicine has the potential to decrease the financial burden of postoperative outpatient care for families of pediatric surgical patients. The purpose of this study was to determine travel and work-related costs related to pediatric surgical clinic visits and parents’ attitudes towards utilizing telemedicine.

Methods: A non-random sample comprised of parents of patients presenting to our outpatient pediatric surgery clinic for postoperative, preoperative, and new consults were administered a previously published 29-question survey that aimed assess the burden of attending clinic, while also querying their preferences towards telemedicine for postoperative care. Pearson chi-square test and univariate logistic regression were used for statistical analysis.

Results: Among 186 survey respondents, most were Hispanic (n=125) followed by non-Hispanic white (NHW) (n=31), non-Hispanic black (NHB) (n=14) and 16 other/unknown. Eighty-one (44%) parents traveled < 25 miles, 78 (43%) traveled between 26-50 miles, and 24 (13%) traveled > 50 miles. The majority of respondents (n=58, 33%) spent $25 to $50 on travel and additional ancillary expenses. Regarding telemedicine in the form of video conferencing for postoperative care, most parents were comfortable using telemedicine to discuss general questions that arose (n=122, 75%) and for routine follow-up (n=94, 56%). Fewer parents were comfortable with the use of telemedicine to assess acute problems (n=72, 45%). Comfort in using telemedicine for postoperative care was not associated with perceived total costs, distance traveled, education level, income level, race, or age. The strongest predictor for comfort in using telemedicine for postoperative care was being comfortable communicating by email and/or telemedicine to discuss medical issues. Spanish-only speaking parents were significantly more likely than English speaking parents to be comfortable using telemedicine for routine postoperative follow-up (OR 2.17; 95% CI 1.01-4.61). There was no significant difference between Spanish-only speaking parents and English-speaking parents when assessing comfort with using telemedicine for acute problems (OR 1.7; 95% CI 0.79-3.65) or general questions (OR 0.88; 95% CI 0.38-2.02).

Conclusion: Clinic visits result in significant costs for parents of pediatric surgical patients. Overall, comfort in using communication technologies was the strongest predictor for comfort using telemedicine for postoperative care. Spanish-only speaking parents were more likely to
be comfortable using telemedicine for routine postoperative follow-up as compared to English-speaking parents.
**ABSTRACT**

Mathematical Modeling of Tumor Response to Ipilimumab Therapy

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Sponsored by:  
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Supported by:  
Vittorio Cristini; McGovern Medical School SRP

Key Words:  
Immunotherapy; mathematical modeling; cancer

Immunotherapy has proven to be a novel approach in the treatment of various cancer types; it expounds upon the strength of one’s own immune system. However, inter-patient and inter-tumor heterogeneity is highly relevant in the case of immunotherapy response: drugs like ipilimumab drive significant improvement in some patients while proving to be futile in others. The complex growth kinetics of each tumor, as well as the “innate strength” of the patients’ immune system, can cause dramatic variances in tumor response to ipilimumab therapy. It is crucial to create a robust mathematical model that can quantify these patient responses to ipilimumab and other immunotherapies in order to understand tumor growth and predicting patient response to therapy.

We incorporated three basic parameters (\(\alpha\), \(\Lambda\), and \(\mu\)) in the mathematical model to predict tumor response over time. We used a nonlinear differential equation for tumor mass over time:

\[
\frac{d\rho}{dt} = \alpha \rho - \rho [1 + \Lambda (\rho - 1)] \mu
\]  

(S1)

where \(\rho\) is the dimensionless tumor mass (ratio of tumor mass over initial tumor mass); \(\alpha\) is the proliferation rate of tumor growth in absence of treatment [s\(^{-1}\)]; \(\Lambda\) is an abstract term that depends on the number of immune cells required to kill one tumor cell and the ratio between initial tumor mass and immune cell count, and \(\mu\) is the efficacy of the immunotherapy treatment in activating immune cells [s\(^{-1}\)].
ABSTRACT

Quantifying the Physiologic Effects of Neoadjuvant Chemoradiation on Patients with Carcinoma of the Esophagus by Integrative Cardiopulmonary Exercise Testing (CPET)

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Sponsored by: Anh Q. Dang, MD, Department of Anesthesiology & Perioperative Medicine, University of Texas M.D. Anderson Cancer Center, Houston, Texas

Supported by: Bernhard Riedel, MD; Shital Vachhani, MD; Benjamin Arnold, MD; January Tsai, MD; Teresa Moon, MD; Jonathan Wilks, MD; Curtis Hightower, MD; Mike Hernandez, MS

Key Words: CPET, Esophagectomy, Cardiotoxicity, Post-Surgery

Background: Esophageal carcinoma patients are commonly placed on a multimodal treatment regimen that includes chemoradiation and surgery. However, the high number of side effects associated with chemoradiation can be detrimental to cardiopulmonary physiology. In the past a patient’s physiologic status following therapy has been measured using single organ assessments such as electrocardiogram and pulmonary function tests. However, CPET is now being used to more accurately integrate the cardiorespiratory and skeletal muscle systems. This study aims to use CPET to determine the effects of chemoradiation on the pathophysiologic state of esophageal carcinoma patients.

Methods: Eight patients underwent CPET prior to neoadjuvant chemoradiation therapy and again following therapy. CPET analysis was performed using cycle ergometer (pedaling at 60 rpm, 15-25 w/minute ramp protocol). Statistical analysis included paired students t-test and post hoc Bonferroni corrections.

Results: The heart rate at peak exercise, hemoglobin, weight, and respiratory function tests (minute ventilation, maximal forced expiratory and inspiratory flow rates) were unchanged following neoadjuvant chemoradiation. There was an increase in the baseline heart rate following neoadjuvant therapy from 65±11 to 75±13 beats per minute (p=0.05). There was a significant decrease in both the % predicted anaerobic threshold from 88±14 to 74±6 (p=0.01) and % predicted peak oxygen consumption from 81±11 to 71±9 (p<0.0001). There was a significant decrease in ΔVO2/ΔWR, a predictor of cardiac output, from 10.1±1 to 9.0±1 following neoadjuvant therapy (p=0.0013). Oxygen pulse, a predictor of stroke volume, was significantly decreased for unloaded cycling, AT, and peak exercise (p=0.02).

Conclusion: These data suggest that neoadjuvant chemoradiation in patients with esophageal carcinoma lead to acute cardiotoxicity without detriment to respiratory function. For future research, CPET can be used to assess physical status in patients with esophageal carcinoma who undergo neoadjuvant chemoradiation to determine whether these measures correlate with post-surgical complications.
ABSTRACT

The Pharmacokinetic Effects of Fucoidan on Chemotherapeutic Regimens

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Sponsored by: Judith A. Smith, B.S. Pharm.D., BCOP, CPHQ, FCCP, FISOPP, Department of Obstetrics, Gynecology, and Reproductive Sciences
Supported by: Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP
Key Words: Fucoidan, cancer, chemotherapy, pharmacokinetics

Background: Fucoidan is a polysaccharide that is extracted from certain species of brown seaweed and marine invertebrates. Preclinical studies have indicated that fucoidan may exhibit antitumor and immunomodulatory properties that can benefit cancer patients. Before such bioactive properties can be investigated, this study sought to identify potential interactions between fucoidan and chemotherapeutic regimens, as well as to determine if supplementation alters chemotherapy pharmacokinetics. Fucoidan has extremely limited bioavailability when administered as an oral supplement, therefore, the supplement would have little to negligible pharmacokinetic effects on chemotherapy.

Methods: This study will compare the pharmacokinetics and adverse effects of selected chemotherapy regimens alone to the same parameters with fucoidan supplementation. A total of ten patients receiving paclitaxel with carboplatin and ten patients receiving 5-fluorouracil with Oxaliplatin (FOLFOX) at the Memorial Hermann Cancer Center. Study subjects were randomized to take fucoidan supplements before Cycle 1 or Cycle 2 of chemotherapy. Pharmacokinetic blood samples were collected during these infusions and analyzed. Toxicity and compliance with regular supplementation were also monitored over the course of patient participation in this study.

Results: This study is ongoing with anticipated enrollment to conclude in October 2017. To date, four patients on the paclitaxel-carboplatin regimen and two patients on the FOLFOX regimen have been enrolled. Toxicities and adverse effects are actively monitored during chemotherapy cycles with and without fucoidan, and, thus far, no differences in adverse effects attributed to chemotherapy have been observed. Analyses of potential differences in pharmacokinetic profiles of chemotherapeutic agents with and without fucoidan supplementation are ongoing and will be presented during a poster session.

Conclusion: Future studies should evaluate the bioactive properties of fucoidan in cancer patients to further elucidate its potential benefit as an adjunct to chemotherapy. Hopefully, this initial pharmacokinetic evaluation will encourage future study of the benefits of fucoidan for cancer patients and its potential to improve quality of life and health outcomes.
ABSTRACT
Impact of Fibrinolytic Phenotype on Outcomes in Thermally-Injured Patients

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Sponsored by: Bryan A Cotton, MD, Charles E Wade, PhD, Todd F Huzar, MD
Supported by: McGovern Medical School Department of Surgery; CeTIR
Key Words: Fibrinolysis shutdown, hyperfibrinolysis, burns, thromboelastrography

Introduction: Fibrinolysis is the physiologic destruction of fibrin clots following their formation that serves to keep microvasculature open and functional. Both extremes of this process, hyperfibrinolysis and fibrinolysis shutdown respectively, have been associated with increased mortality in both adult and pediatric trauma populations. We hypothesized that these fibrinolytic phenotypes occur in patients with thermal injuries and are associated with increased resuscitation volumes, complications, and mortality.

Methods: A retrospective analysis was performed on patients admitted to the John S Dunn Burn Center at Memorial Hermann between 01/2009 and 12/2016 with age ≥ 18 years, TBSA ≥ 20%, and a survival ≥ 24 hours post admission. Patients were first divided into three groups representing their fibrinolytic states using a quantitative indicator of percent clot lysis at 30 minutes (LY30) determined by thromboelastography. LY30 ≤ 0.9% indicates fibrinolysis shutdown (SD), 0.9% to 2.9%, physiologic fibrinolysis (PHYS), and ≥ 3%, hyperfibrinolysis (HF). Univariate and multivariate analyses were performed.

Results: Of 145 patients who met the inclusion criteria, 48% presented with SD while 36% presented with PHYS and 16% with HF. Both SD and HF patients had higher base deficits than those with PHYS [(median 9 (6, 2) and 8 (7, 2) vs. 3 (6, 1); p = 0.006) and received more fluids during 24-hour resuscitation [(median 3.3mL/kg/TBSA (2.4, 4.3) and 3.5 (2.9, 4.4) versus 2.6 (2.1, 3.6); p = 0.008)]. While there was a trend towards higher mortality and occurrence of sepsis and respiratory failure in patients with SD (versus PHYS or HF), this was not statistically significant. (TABLE) When controlling for age, gender, %TBSA, and inhalation injury, SD patients were 3.5 times more likely to experience in-hospital mortality than patients presenting with the PHYS or HF phenotypes (OR 3.56, 95% C.I. p = 0.031).

Conclusions: In severely burned patients, shutdown is the most common fibrinolytic phenotype and is associated with a three and a half-fold increased risk of mortality. Shutdown patients also appear more likely to develop respiratory failure and sepsis compared to physiologic and hyperfibrinolytic patients.

<table>
<thead>
<tr>
<th></th>
<th>Shutdown (n=69)</th>
<th>Physiologic (n=52)</th>
<th>Hyper (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>30%</td>
<td>21%</td>
<td>17%</td>
<td>0.190</td>
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<tr>
<td>Respiratory failure</td>
<td>32%</td>
<td>21%</td>
<td>13%</td>
<td>0.065</td>
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<tr>
<td>Acute kidney injury</td>
<td>49%</td>
<td>32%</td>
<td>50%</td>
<td>0.067</td>
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<tr>
<td>In-hospital mortality</td>
<td>39%</td>
<td>23%</td>
<td>29%</td>
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ABSTRACT

Safety of robotic assisted laparoscopic recurrent paraesophageal hernia repair: Insights from a large single institution experience

Nicholas F. Holton  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Shinil K. Shah, DO, Minimally Invasive and Elective General Surgery
Supported by:  Shinil K. Shah, DO, Minimally Invasive and Elective General Surgery
Key Words:  Robotic surgery; Paraesophageal hernia; Recurrence

Background: Laparoscopic repair of recurrent as opposed to primary paraesophageal hernias (PEH) are associated with increased peri-operative complication rates, worse outcomes, and increased conversion rates. The robotic platform may aid surgeons in these complex revisional procedures. Our aim was to compare the outcomes of patients undergoing robotic assisted laparoscopic (RAL) repair of recurrent as opposed to primary PEHs.

Methods: Patients undergoing RAL primary and recurrent PEH repairs from 2009-2017 performed at a single institution were reviewed. Demographics, use of mesh, estimated blood loss, intra-operative complications, conversion rates, operative time, rates of esophageal/gastric leak, hospital length of stay, readmission/re-operation rates, recurrence, dysphagia, gas bloat, and pre- and post- operative proton pump inhibitor (PPI) use were analyzed. Analysis was performed using the appropriate parametric or non-parametric analysis (continuous data) or Pearson’s Chi-squared test or Fisher’s exact test (categorical data).

Results: There were 325 patients who underwent RAL PEH repairs (265 primary, 60 recurrent) and were followed for a median (range) of 121 (5-2592) days. In the recurrent PEH group, patients had a median (range) of 1 (1-3) previous PEH operations. There were no differences in baseline demographics (age, body mass index, American Society of Anesthesiologists score, gender, insurance status, marital status, race/ethnicity, and pre-operative PPI use) between the groups. More patients in the recurrent PEH group had previous abdominal surgery (96.7% versus 68.3%, p<0.001), were more likely to have mesh placed (50% versus 34%, p=0.03), had longer operative times (170.4 versus 137.0 minutes, p=0.0006) and had longer hospital length of stay (66.2 hours versus 43.8 hours, p=0.001). Intra-operative complications, estimated blood loss, readmission and re-operation rates, recurrence, post-operative dysphagia and gas-bloat, and post-operative PPI use were not significantly different between the groups. There were no conversions or gastric/esophageal leaks in either group.

Conclusions: Although associated with longer operative times and hospital length of stay, RAL recurrent PEH repairs have similar perioperative and post-operative outcomes as compared to primary PEH repairs. Whether this is secondary to potential advantages afforded by the robotic platform deserves further study.
ABSTRACT

Geographic, Financial, and Social Burdens of Care in Families of Pediatric Cancer Patients

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Sponsored by: Mary Austin, M.D., M.P.H.
Supported by: The Department of Pediatric Surgery, McGovern Medical School at UTHealth
Key Words: Pediatric Cancer, Burden of Care

Health disparities in adults with cancer have been shown to significantly impact treatment outcome. However, health disparities are much less defined in the pediatric population. Additionally, financial, geographic, and racial disparities have each been independently correlated with increased burden of cancer treatment, but the impact of these burdens in families of children with cancer is poorly understood. Our objective is to develop and administer a cross-sectional survey to identify financial, social, and geographical barriers to care and describe their associated burden on parents and caregivers of children undergoing cancer treatment at M.D. Anderson Cancer Center (MDACC). The protocol for this study is currently undergoing IRB approval. The survey will be developed using a mixed methods approach, including the Impact on Family (IOF) scale and cancer-specific questions. The IOF scale is a survey instrument used to measure the impact of chronic childhood illnesses on families. Cancer-specific questions will be derived from semi-structured interviews conducted on 20 parents of children with cancer. Additionally, cognitive interviews will be conducted on another group of survey participants and exploratory factor analysis will be run. The survey items will be translated into Spanish, undergo linguistic validation, and administered to a final group of 200 participants. Finally, confirmatory factor analysis will be run to evaluate the validity of the cancer-specific questions. The selection of all participants will be non-random and purposeful to insure enrollment of a diverse study population reflective of the pediatric oncology patient population at MDACC. From their survey results, participants will each be given a comprehensive IOF score and dichotomized into a high impact or non-high impact group, revealing demographic characteristics associated with highly impacted families. The data acquired from this project will help identify the burdens that families of pediatric patients face when undergoing treatment, add to our understanding of health disparities in children and adolescents with cancer, and identify determinants of families at risk of significant burden to inform the development of supportive interventions.
ABSTRACT
Magnesium Sulfate Infusion During Fetal Meningomyelocele (fMMC) Repair to Reduce the Dose of Inhalational Anesthesia

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Sponsored by: Roopali Donepudi, MD, Department of Obstetrics, Gynecology, and Reproductive Medicine
Sponsored by: Ranu Jain, MD, Department of Anesthesiology
Keywords: Inhalation anesthetics, sevoflurane, magnesium sulfate, myelomeningocele, spina bifida, in utero repair surgery, second trimester

BACKGROUND: Fetal myelomeningocele (fMMC) is a congenital defect in the vertebral column with herniation of the meninges and spinal cord in a sac-like protrusion. During the second trimester, this condition can be surgically treated through open fetal surgery, requiring profound uterine relaxation, fetal anesthesia, uterine tocolysis, and general anesthesia. However, animal model studies on general anesthesia using inhalational anesthetics have shown neurodevelopmental deficits and is not well studied in human fetuses. Sevoflurane, an inhalational anesthetic, is used in fMMC repair for both general anesthesia and uterine relaxation. Magnesium sulfate is a tocolytic that is administered during surgery to prevent contractions post-surgery. The objective of this study was to determine if starting magnesium sulfate (MgSO4) infusion at maternal skin incision during surgery, rather than at uterine closure, would reduce the requirement of inhalational anesthetic agents in fMMC repair.

METHODS: This is a prospective observational study of in-utero fMMC repair performed from September 2011 to August 2017. Comparison was performed between two groups: Group 1 - MgSO4 at uterine wall closure (September 2011 to January 2016), and Group 2 - MgSO4 at maternal skin incision (February 2016 to August 2017). 6 grams loading dose followed by 2 grams/hr of MgSO4 were given in all cases. The inhalational agent was titrated up until adequate uterine relaxation was attained, which was determined by the surgeon on palpation. Maternal demographics, anesthetic agents used during fetal surgery, intraoperative complications, and pregnancy outcomes were reviewed.

RESULTS: 53 patients were enrolled in the study; anesthesia records were available for 51 patients. There were 30 patients in Group 1 (uterine closure) and 21 patients in Group 2 (maternal skin incision). Average gestational age at surgery was 25.02 weeks (± 0.6). Average gestational age at delivery was 34.1 weeks (± 3.5). Both groups had 3 patients in which severe hypotension occurred that required treatment with ephedrine. Average MAC of sevoflurane was 1.53 (± 0.16) for Group 1 and 0.96 (± 0.22) for Group 2 with a p-value of <0.0001. Average phenylephrine rate and surgical time were not significantly different.

DISCUSSION: MgSO4 has been used for tocolysis to provide uterine relaxation following fetal repair. We found that early initiation of MgSO4 infusion at maternal skin incision was associated with lower inhalational anesthesia administration. There has been growing concern with the effects of high doses of these agents on long-term fetal neurodevelopmental outcomes. Using magnesium sulfate earlier may reduce the total exposure to the fetus.
ABSTRACT

Turner Syndrome: Karyotype and Severity of Associated Comorbidities

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Sponsored by: Siddharth Prakash, M.D., Ph.D., Dept. of Internal Medicine

Supported by: Siddharth Prakash, M.D., Ph.D., Dept. of Internal Medicine

Key Words: Turner Syndrome, Bicuspid Aortic Valve, Aortic Dilatation

TS is a common chromosomal disorder that affects approximately 1 in 2500 live female births. Complete or partial monosomy of one of the X chromosomes in a female is associated with various congenital heart defects (CHDs), which include aortic dilatation, coarctation of aorta, and BAV. Congenital cardiovascular defects related to BAV are the leading cause of death in TS women. The Turner Syndrome Network Registry (TRN Registry) and genetic sample repository can help address the lack of knowledge behind these CHDs by facilitating the recognition of demographic and genetic patterns in TS patients. This study compares frequency and severity of associated comorbidities between Turner Syndrome (TS) patients of mosaic (45,X/46,XX & others) and non-mosaic (45,X) karyotypes. TS patients were recruited into the TRN Registry, and gave blood and saliva samples after informed consent. Chromosomal microarrays were analyzed to confirm the genetic diagnosis and ascertain the karyotype. Demographic, socioeconomic, and medical history of our patients were abstracted from questionnaires and follow-up of medical records. ECGs, CT, MRI, and echocardiogram images were analyzed to determine the prevalence and severity of additional cardiovascular defects in the TS cohort. Since the establishment of the TRN Registry, 32 patients were identified and recruited. 26 patients had their karyotype confirmed: 13 had mosaic karyotype, and 13 had 45,X karyotype. Comparison of patients based on karyotype revealed there was not a statistically significant difference in the tested variables between mosaic and 45,X TS patients, confirmed by 2 tailed t tests with P > 0.05. Blood pressure measurements for 45,X and mosaic TS patients revealed: a) average systolic blood pressure was 116 mmHg and 118 mmHg, respectively (P = 0.142); b) average diastolic blood pressure was 76 mmHg and 77 mmHg, respectively (P = 0.224). Bloodwork for 45,X and mosaic TS patients revealed: a) average eGFR (corrected for gender and age via MDRD equation) was 163.45 mL/min/1.73m² and 120.39 mL/min/1.73m² respectively (P = 0.212); b) average HbA1C was 5.31 and 5.25, respectively (P = 1.0); c) average LDL was 87 and 98, respectively (P = 0.338). Fifteen ECG measurements for 45,X (8) and mosaic (7) TS patients revealed: a) average QTc interval was 437 msec and 453 msec, respectively (P = 0.381); b) average PR interval was 129 msec and 129 msec, respectively (P = 0.894); c) average QRS duration was 79 msec and 86 msec, respectively (P = 0.292). Data from the TRN registry revealed there was no statistically significant difference in blood pressure, ECG measurements, and lab values between 45,X and mosaic TS patients. Most members of the TS cohort were host to a wide array of CHDs, renal, reproductive, and chronic conditions. Among the more common complications were the CHDs (especially BAV). The higher frequency of these conditions predisposed TS patients to many cardiovascular complications, the most drastic being aortic aneurysms. Future research should stress the importance of patient education and active management of cardiovascular risk factors from an early age.
ABSTRACT

Using Client Language to Explore Mechanisms of Change in an Experimental Therapy for Comorbid Substance Use and Post-Traumatic Stress

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Sponsored by: Margaret Wardle, Ph.D., UTH Psychiatry Department
Supported by: The Saltzberg Fellowship Award
Key Words: Language, Therapy, PTSD, SUD

Background and Significance: Co-occurrence of post-traumatic stress disorder (PTSD) and substance use disorder (SUD) is associated with more severe SUD and lower success rates for SUD treatment. A novel treatment recently developed in our research group integrates cognitive processing therapy, an evidence-based treatment for PTSD, with standard cognitive behavioral therapy (CBT) for SUD in an attempt to improve treatment outcomes for comorbid SUD/PTSD. Developing more effective therapies requires identifying and refining the mechanisms at work during therapy as well as targeting therapies to individuals for whom that mechanism is relevant or effective. Although treatment outcome metrics are often standardized, few tools exist to analyze mechanisms active during therapy sessions. The Linguistic Inquiry and Word Count (LIWC) program measures use of speech categories, such as “negative emotion” and “past focus”, allowing objective quantification of language used in therapy, and thus objective indicators of topics and processes addressed in therapy sessions.

Hypothesis: With standard CBT for SUD as a comparator, we expected the novel therapy to evoke significantly higher levels of emotional engagement, as measured by the use of positive and negative emotion words. We also expected that patients’ distress tolerance, defined as the ability to weather adverse emotions, would correlate with emotional engagement in therapy and would prove particularly important to emotional engagement in the novel treatment. Finally, we explored the predictive capacity of language use for treatment outcomes.

Experimental Design: We analyzed language use during critical therapy sessions in a randomized, controlled trial in which patients with both PTSD symptomatology and SUD were assigned to either the novel integrated treatment or standard CBT for SUD alone. Transcripts of therapy sessions were analyzed by the LIWC and compared using (1) independent sample t-tests comparing emotion language across therapies and (2) moderated regressions examining the effects of distress tolerance on emotion language in each therapy. Finally, theoretically relevant LIWC categories were used as independent variables in exploratory regressions predicting treatment outcome scores.

Results: Unexpectedly, negative emotion language did not differ significantly between the two therapies. Instead, there was more use of positive emotion language in the standard therapy. Positive emotion language use in the standard therapy was further increased in patients with higher baseline distress tolerance. Finally, more use of positive language was associated with better PTSD, although not SUD, outcomes.

Conclusions: We concluded that positive emotional engagement, measured by positive emotion language, was actually higher in the standard therapy, that distress tolerance increased positive
emotion in therapy, and that positive emotion correlated with observed treatment outcomes. Future research should explore methods of increasing distress tolerance to experimentally determine effects on both emotional engagement in therapy and treatment outcomes.
ABSTRACT
Student Attitudes and Perspectives on Social Determinants of Health in Preclinical Medical Education

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Sponsored by:  Rebecca B. Lunstroth, JD, MA, McGovern Center for Humanities and Ethics
Key Words:  Social determinants of health, medical education, social disparities

It is becoming increasingly apparent that in addition to being knowledgeable in basic sciences and clinical skills, medical students are also required to be knowledgeable in the social contexts that influence the course of disease. In order to best educate the future leaders of healthcare, we wanted to learn more about our student body. The purpose of this study was to determine if there is a correlation between student demographics and their attitudes on social determinants of health in the medical school curriculum. A voluntary and anonymous survey was distributed through email to the student body of McGovern Medical School and assessed student confidence and attitudes about working with patients affected by social determinants of health and learning about the subject matter in the current curriculum. Responses were recorded on a five-point Likert scale. Out of 89 participants in the survey, our results showed a significant portion of students who were first generation college graduates were more confident in working effectively with disadvantaged populations as well as students who had previously worked with a community-based organization. We found that other demographics, such as gender, race, and religion, showed no significant correlation on student attitudes towards social determinants of health. With this information we plan to create more educational experiences that expose students to social determinants of health in multiple educational modalities in order to increase student confidence prior to clinical clerkships.
ABSTRACT

Can we trust the clinic diagnosis of hypertension in pediatric patients with respect to White Coat Syndrome?

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Sponsored by: Joshua Samuels, MD, MPH
Supported by: NIH/NIDDK
Key Words: White coat hypertension, masked hypertension, hypertension, pediatrics

Along with the recent obesity epidemic in the United States, we have seen the pediatric distribution of blood pressure (BP) level shift towards higher values. This elevated BP in children has been shown to be associated with increased incidence of early markers of atherosclerosis such as left ventricular hypertrophy. Making an accurate diagnosis could subsequently lead to better and more efficient care with respect to hypertension. We followed up on a previous 2001 study titled Evaluation of white coat hypertension in children to determine any increase or decrease in the prevalence of white coat hypertension seen at the UTHealth pediatric hypertension outpatient clinics.

A retrospective chart review was conducted of 219 pediatric hypertension patients born after 1995 assessed by 24-hour ambulatory blood pressure monitoring (ABPM) at the UTHealth pediatric hypertension clinics from January 1st, 2015-December 31st, 2016. Our study found white coat hypertension to be present in only 13% of our subject pool. Masked hypertension was found in 12% of the population. The overall concordance rate of clinical and ambulatory BP (not white coat, masked, or missing American Heart Association (AHA) classification) was 63%. After controlling for all other covariates, concordance was associated with higher clinical systolic blood pressure (SBP) or diastolic blood pressure (DBP) and younger age.

Past research suggests varied prevalence regarding white coat hypertension (0.6-88%) and a more narrow range of reported masked hypertension (7.6-15%). Our study suggests that the rate of white coat hypertension seen in our local population is markedly less than most reported statistics found in the literature. However, we saw a 12% prevalence of masked hypertension which is in line with previous estimates. Although hypertension has been widely studied in adults, there are fewer published studies employing ABPM in the pediatric population. With these results, more accurate evaluation and treatment of hypertension can be administered in children.
ABSTRACT

Obesity Association with Breast Cancer Related Lymphedema

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Sponsored by: NIH R01 CA201487, NIDDK 2 T35 DK007676-22
Supported by: Melissa Aldrich, PhD, Eva Sevick, PhD, UTHealth Center for Molecular Imaging
Key Words: Breast cancer related lymphedema, obesity, inflammation, chemotherapy

Breast cancer-related lymphedema (BCRL) is a progressive disease encountered by up to 40% of breast cancer survivors, currently numbering more than three million women in the United States (1.2 million with BCRL). BCRL is characterized by swollen arms and trunks, frequent cellulitis attacks, pain, and depression. BCRL can appear at any time after cancer treatment, even years later. BCRL occurs more frequently in patients receiving axillary lymph node dissection (ALND) and radiation treatment, but the etiology is unknown. A potential risk factor for BCRL may be obesity. The relationship between fat cell growth and lymph stasis is well known—stagnant lymph provides molecular factors to adipose cells that encourage growth and multiplication. In this project, the relationship between ghrelin, leptin, and adiponectin (markers of obesity) to lymphatic pulsing was explored.

Blood samples were taken and plasma levels for ghrelin and leptin were measured using commercial ELISA kits. Although the sample size was 10 subjects, we expect to see trends that will be reflected in the larger, full-study sample size of 100 study subjects. Lymphatic pulsing was recorded using NIRFLI technology and was loaded into ImageJ software (NIH) for analysis. Images were evaluated for lymphovascular anomalies and lymphatic pulsing frequencies (pulses per minute).

After analyzing the pulsing and ELISA data for leptin, ghrelin, and adiponectin, slight trends were observed. It’s expected these trends would be stronger if the full study of 100 subjects was analyzed. Before conducting the experiment, it was expected that impaired lymphatic function (decreased pumping) would be correlated with obesity markers, like higher leptin and lower adiponectin and ghrelin. The results showed that 7/10 patients had marked decreased lymphatic pumping in their affected arm than the normal arm, which goes to show that breast cancer surgery can impair lymphatic function. Overall, adiponectin decreased with higher pulsing, which was unexpected. We hypothesized that higher adiponectin would correlate with higher pulsing, because typically, the higher these values are, the healthier the subject is. Leptin increased with higher pulsing, which was also unexpected, as we would expect leptin values to decrease with higher pulsing. Ghrelin values did not have an obvious trendline. Although the results were not anticipated, observing specific trends will better help us identify possible risk factors for developing BCRL in the future.
ABSTRACT

Functional Engraftment of Airway Basal Stem Cells for Future Cystic Fibrosis Therapy

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Class of 2020

Sponsored by: Dr. Brian R. Davis
Supported by: Dr. Brian R. Davis, and the McGovern Medical School Dean’s Office
Key Words: Cystic Fibrosis, Basal Cells, Mouse Model

Cystic fibrosis is an autosomal recessive genetic disease that affects 1 out of 3000 individuals. Mutations in the CFTR gene causes the transcription and translation of a non-functional chloride channel that is necessary to mediate fluid flow by creating an osmotic gradient. CFTR-mediated fluid flow is critical to the production of sweat, pancreatic enzymes, and mucus, and the loss of CFTR functionality leads to pathology of CF. Although CF affects a variety of organs (e.g. lung, pancreas, and intestine), it is the loss of lung mucociliary clearance that is the primary driver of morbidity and mortality. Gene editing technologies have made it possible to correct the CFTR gene in vitro but delivering the corrected protein to living individuals remains an area of investigation. Basal cells are a stable population of stem cells that reside in the respiratory epithelium of the lung, and are able of giving rise to all the cell lineages that normally make up the epithelial layer. Thus, delivery of CFTR corrected basal cells could act as an efficient vehicle to provide functional CFTR to cystic fibrosis patients.

In an effort to establish an airway basal cell engraftment model we first established a model of mouse airway injury. Mice were treated with naphthalene IP at 160-380 mg/kg body weight. Two days post treatment, lungs were collected and immunostained for basal and secretory cell markers (K5 and CCSP, respectively). Naphthalene injury led to a reduction in basal cell numbers in the trachea where they reside, and a total denuding of secretory cells from the conducting portions of the lungs. The murine lung K5+ basal cells showed healing at days 2, 4, and 14 post treatment, with basal cells reconstituting in the trachea first, then moving into the mainstem bronchi. By day 14, the K5+ basal cell distribution and intensity was similar to untreated samples. CCSP+ secretory cells did not recover even by day 14.

Human airway basal cells were labelled then delivered to naphthalene-injured mice. We expanded human airway basal cells in dual-SMAD inhibition media (Mou et al, 2016), then labeled the basal cells with GFP-lentivirus. These cells were then FACS sorted to enrich for the GFP+ population. GFP+ labelled human basal cells were delivered to mice 2 days post treatment with 275 mg/kg naphthalene body weight. Mice were euthanized and lungs collected at day 2. Sections were first analyzed for GFP, then stained for Laminin A&C (human nuclear envelope proteins) to assay for cell engraftment. Preliminary results gives evidence for some presence of human cells in the injured mouse airway.

Here we have developed a system to culture, manipulate, and label human airway basal cells for transplant. We have also laid the groundwork for introduction into a mouse model by showing damage to the mouse respiratory epithelium in response to naphthalene treatment. In the future,
this system and methods could be used for gene therapy and live modeling of airway diseases, Cystic Fibrosis for example, which is amendable to genetic editing.
ABSTRACT

Development of a New Cellular Model of Cluster Headache: Primary Mouse Trigeminal Ganglia Cultures as a Treatment Model

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Sponsored by:  
Mark J. Burish, M.D., Ph.D., Vivian L. Smith Department of Neurosurgery

Supported by:  
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Key Words:  
Cluster headaches, circadian, trigeminal ganglia

Background: Cluster headaches commonly demonstrate a clock-wise regularity in symptom onset, with 82% of patients having headaches at the same time of the day and 12% at the same time each year. This suggests an association between cluster headaches and potential circadian abnormalities. Furthermore, there has been evidence that some of the more effective therapeutic treatments for cluster headache prevention may modulate the circadian cycle, for example expression levels of the Period2 gene. Unfortunately, current treatments are ineffective for many patients. Thus, the development of neuronal models is important to explore the effects of other treatments on circadian expression, with the ultimate goal of identifying new treatments for cluster headache.

Methods: Trigeminal ganglia were harvested from transgenic mice expressing Period2::Luciferase, in which the amount of light released can be used as a marker of Period2 gene expression. The ganglia underwent enzymatic digestion in a papain solution followed by a dispase and collagenase IV solution. The digested ganglia were subsequently passed through a 100 uM filter to remove undigested debris. The isolated neurons were then plated with F-12 culturing media onto 35 mm dishes, treated in advance with poly-d-lysine and laminin to promote adherence. The neuronal cultures were incubated at 37° C and media was changed at 24 hours following initial seeding to remove residual debris. Neuronal cultures confluent at 72 hours following initial seeding were treated with dexamethasone for 1 hour to synchronize the circadian rhythms. Following synchronization, the culture media was replaced with recording media containing luciferin and placed into a lumicycle. The real-time luminescence of each neuronal culture was recorded over a 72-hour period or after 3 periods of oscillation. The cultures were then treated with either 3 uM or 10 uM verapamil and placed back into the lumicycle to observe any associated circadian effects.

Results: The trigeminal ganglia dissociation showed promising results, as the initial seeding produced confluent cultures. These cultures also displayed an observable oscillatory pattern in the lumicycle after synchronization and application of recording media. Interestingly, treatment with 3 uM and 10 uM verapamil (a cluster headache preventive medication) appeared to decrease and increase the amplitude of oscillation, respectively. However, due to low sample size, no significant deviation could be calculated.

Conclusion: Primary mouse trigeminal ganglia cultures are a promising field for examining the effects of cluster headache treatments on circadian rhythms. Despite a lack of sample size necessary for significance, circadian rhythms and associated modulation were observable.
ABSTRACT

Identification of Quorum Signaling Response Elements in \textit{C. difficile} strain 630

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Sponsored by: Charles Darkoh, PhD, UTHSC School of Public Health, Center for Infectious Disease

Supported by: Charles Darkoh, PhD, UTHSC School of Public Health, Department of Epidemiology, Human Genetics and Environmental Sciences, Center for Infectious Disease; Office of the Dean

Key Words: \textit{C. difficile} 630, quorum signaling, Agr, TI signal

\textbf{Background:} \textit{Clostridium difficile} is one of the most commonly acquired nosocomial infections in the United States, with its incidence increasing over the last several decades. This enteropathogen causes disease by producing toxins A and B. These toxins have become promising targets for therapy due to the propensity of \textit{C. difficile} to develop antimicrobial resistance. Toxin synthesis is regulated by an accessory gene regulator (Agr) quorum sensing system, which is mediated by a thiolactone signal (designated as TI). There are two physically separated Agr systems within the \textit{C. difficile} genome, which are designated Agr1 and Agr2. Agr1 is present in all sequenced strains and only encodes genes required for TI signaling. However, Agr2 is present in hypervirulent strains and contains genes required for both TI signal synthesis and response, which is necessary for toxin production activation. Surprisingly, \textit{C. difficile} strain 630 encodes only the Agr1 locus and lacks Agr2, but is still able to synthesize toxin. This suggests that 630 utilizes unidentified non-Agr designated genes to sense and respond to the TI signal. We hypothesized that 630 utilizes a two-component system, comprised of a histidine kinase and a response regulator, to respond to the TI signal. We anticipate that this two-component system may be transcriptionally regulated by the TI signal.

\textbf{Methods:} \textit{C. difficile} strain 630 was incubated both with and without TI signal for 4 hours, and a toxin assay was performed to confirm that only the 630 exposed to TI signal produced toxin. RNA was extracted and subsequently used to synthesize cDNA. Quantitative real-time PCR was performed using the cDNA to assess expression levels of 42 pairs of two-component systems present in the genome of the 630 strain. Quantification cycles (Cq) were compared to determine relative expression of target genes in TI-incubated 630 compared to 630 not exposed to TI.

\textbf{Results:} No single gene target showed significant overexpression based on Cq values in cDNA synthesized from cells exposed to the TI signal compared to the unexposed cells.

\textbf{Conclusions:} Our results to date are inconclusive, as no single two-component system seemed to have significantly increased expression in cells exposed to the TI signal. We plan to repeat the experiment using cDNA synthesized from an Agr1 mutant exposed to the TI signal with the expectation that this causes significant overexpression of the cognate two-component system.
ABSTRACT

Walking Impairment Questionnaire Association to Subclinical Peripheral Artery Disease in the Cameron County Hispanic Cohort

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Sponsored by: Susan P. Fisher-Hoch, MD
Supported by: NIH/NIDDK: 5 T35 DK 7676-24; Bruce C. Kone, MD
Key Words: Peripheral artery disease, ABI, TBI, walking impairment questionnaire.

Background: Prevalence and associations for Peripheral Artery Disease (PAD) in Mexican Americans (MA) have not been well characterized. The aim of this study was to find functional ability differences between those who have PAD and those who do not using the Walking Impairment Questionnaire in a random population sample of MA adults in Cameron County, Tx.

Methods: Subjects underwent measurement of bilateral ankle and toe brachial indices (ABI, TBI) using a Doppler system in order to identify those with PAD (ABI ≤ 0.9, TBI ≤ 0.7). The higher and lower of the two pedal pressures for each limb were used for calculating ABI-High (Traditional method) and ABI-Low (Sensitive Method), respectively. In addition, toe pressures were used for calculating TBI. The Walking Impairment Questionnaire assesses leg pain symptoms, walking speed, and walking distance. A subject receives a score out of a hundred after each section to describe their function percentage (a lower score points to increased impairment). Questionnaire scores were compared between people that had PAD and those that did not.

Results: Of the 326 participants, 9 subjects were classified as having PAD using the ABI-High definition, 32 subjects had PAD using the ABI-Low definition, and 54 subjects had an Abnormal TBI. Individuals classified as having PAD in the ABI-High and ABI-Low categories did not show a significant difference in the Walking Pain Symptoms score when compared to normal. Nevertheless, subjects with PAD in the ABI-High and ABI-Low categories had significantly lower Walking Speed and Distance scores when compared to normal.

Conclusions: The Walking Impairment Questionnaire could serve as an accessible and affordable tool for early screening of the disease in individuals with subclinical PAD and underlying decreased leg functions. This could lead to a decrease in disease progression by implementing timely risk factor modifications and early interventions or treatments.
Modulation of the function of eIF4F complex by eIF4A inhibition in Merkel cell carcinoma cells: regulation of oncogenes and a new therapeutic implication

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Sponsored by: Stephen K. Tyring, MD, PhD, MBA, Department of Dermatology, McGovern Medical School at Houston
Supported by: Stephen K. Tyring, MD, PhD, MBA, Department of Dermatology and the Office of the Dean, McGovern Medical School at Houston
Key Words: Merkel cell carcinoma, Silvestrol, Survivin, Mcl-1

Background: Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer with rising incidence in immunocompromised patients. The recently discovered Merkel cell polyomavirus (MCPyV) is clonally integrated in over 80% of MCC tumors, and the carcinogenic mechanism of MCPyV is dependent upon activation of mTOR and 4E-BP1 pathways. The former pathways drive carcinogenesis through recruitment of eukaryotic initiation factors (eIFs) and assembly of the eIF4F complex, composed of eIF4A, eIF4E, and eIF4G at the 5'-m7G cap. The direct eIF4A inhibitor silvestrol, previously characterized in other cancer cells, has been found to promote cell cycle arrest, translation inhibition, and autophagy. Such studies noted reduced levels of cyclins B1 and D1, Bcl-2, c-myc, survivin, and Mcl-1; however, if silvestrol has similar implications in the treatment of MCC cells requires further investigation.

Methods: MCC cell lines derived from MCPyV-positive MCC tumors (MS-1 and MKL-1) and MCPyV-negative MCCs (MCC13) were cultured and treated with silvestrol for 24 and 48 hours. Protein lysates were extracted and subjected to SDS-PAGE and Western blot analysis. Antibodies against Mcl-1 and survivin were applied.

Results: We utilized the MCC cell lines, MS-1 and MKL-1 (derived from MCPyV-positive MCC tumors), to analyze the impact of silvestrol on eIF4A. Our data showed that treatment of MS-1 and MKL-1 cells with the direct eIF4A inhibitor silvestrol resulted in marked decreases in downstream oncoprotein expression. Specifically, our data demonstrated that eIF4F complex inhibition resulted in downregulation of survivin and Mcl-1 in both 24- and 48-hour treatment groups. Next, we used an MCPyV-negative MCC cell line (MCC13) to further characterize the impact of eIF4F complex inhibition via silvestrol treatment. Specifically of interest was survivin modulation in the MCC13 cell line, as previous studies have suggested that the oncogene is activated by MCPyV. Interestingly, we found that survivin was markedly downregulated in 24- and 48-hour treatment groups in the MCC13 cell line, too.

Conclusions: Overall, our findings demonstrate that silvestrol's action in blocking eIF4A results in the downregulation of important oncogenes like survivin and Mcl-1 downstream of the eIF4F complex. As the eIF4F complex governs the downstream mechanisms of the mTOR/4E-BP1 axis, crucial for Merkel cell carcinogenesis, our findings may suggest an intriguing novel possibility of utilizing eIF4A inhibitors for treatment of MCCs. Future work should include adjusting silvestrol doses based on IC50 data and carrying out protein profiling assays to better characterize the effect of the treatment on the three cell lines.
ABSTRACT

The Role of IL-6, MCP-1, TLR4 Signal Pathway and MAPK Signal Pathway in Paclitaxel Induced Peripheral Neuropathy

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Department of Pain Medicine

Supported by: NCI R01 CA200263 and the H.E.B. Professorship in Cancer Research

Key Words: CIPN, Paclitaxel, DRG, Cytokines

Paclitaxel is the front-line chemotherapeutic agent used to treat the most common solid tumor cancers, including those of the lung, breast and ovary. Paclitaxel interferes with the growth and division of cancer cells by promoting the assembly of stable but dysfunctional microtubules. Chemotherapy Induced Peripheral Neuropathy (CIPN) is a debilitating and persistent dose-limiting side effect of Paclitaxel treatment. The mechanisms underlying CIPN are extremely complex, therefore comprehensive and cohesive process behind it have yet to be fully elucidated. In vivo studies have provided explanations for many of the processes surrounding CIPN. The aim of this study was to provide further evidence for the mechanisms underlying Paclitaxel induced CIPN by using an in vitro model of Paclitaxel treatment. Cytokines have been identified as key participants in the pathophysiology driving CIPN. The focus of this research is targeted on IL-6 and MCP-1, the TLR4 signal pathway, and the MAPK signal pathway. By providing evidence for their role in an in vitro paclitaxel treated primary rat DRG culture model, we hope to gain a better understanding of the mechanisms behind paclitaxel induced CIPN as well as provide a platform from which potential therapeutics and further research may be based on. In primary rat DRG culture incubated with Paclitaxel, TLR4 and MyD88 were upregulated at 48h, and the immediate down-stream signal molecules Mitogen-activated protein kinases (MAPK), Extracellular signal related kinase (ERK1/2) and p38 but not c-Jun N terminal kinase (JNK), were upregulated at 2h and 48h after paclitaxel incubation using western blot. This upregulation could be prevented by pretreated with TLR4 antagonist (LPS-RS). IL-6 and MCP-1 were released into culture medium detected by using ELISA and upregulated in cultured cells using western blot after paclitaxel treatment. IL-6 and MCP-1 staining was co-localized to TLR4-positive cells using Immunohistochemistry. Whole-cell patch clamp recordings in rat DRG neurons revealed that MCP-1 induced spontaneous action potentials and enhanced the amplitude of membrane potential oscillation. These results implicate that IL-6, MCP-1, TLR4 signaling pathway and MAPK signaling pathway may be important in the induction and maintenance of paclitaxel related CIPN.
ABSTRACT

Tunneled Central Venous Catheters in Pediatric Intestinal Failure Patients: A Single Center Review

ROBERT MARTIN
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Sponsored by: Dr. Kuojen Tsao, MD, Pediatric Surgery
Supported by: Dr. Kuojen Tsao
Key Words: Complications/Contributors to Broviac Complications

Introduction: Children with intestinal failure (IF) often require a tunneled central venous catheter (CVC) for parenteral nutrition. The purpose of this study was to characterize complications after CVC placement and contributors to line loss in IF pediatric patients.

Methods: A retrospective chart review of pediatric (<18 years) IF patients who had a silicone tunneled CVC newly inserted or exchanged over a wire from 2012-2016 was conducted. Patient demographics, catheter insertion service (surgery vs. interventional radiology), procedure type (new vs. exchange), vessel and complications related to CVCs were evaluated. Complications included dislodgement, infection, break or mechanical malfunction, and occlusion. An ethanol lock protocol for silicone CVCs in IF patients was instituted in January 2012. Descriptive statistics, t-test, ANOVA, chi², and linear regression were used for analysis.

Results: 29 IF patients with tunneled CVCs were identified with 191 lines and 17,598 line days. Patients had a median age of 19.7 months (IQR 8.7 – 40.8) at the time of line insertion and had a median of 5 catheters (IQR 2 - 9). Necrotizing enterocolitis was the most common etiology of IF (59%). There were 13.4 complication events per 1000 line days. Line breaks were the most common complication (4.7 events/1000 line days) followed by occlusion (3.4 events/1000 line days), infection (3.0 events/1000 line days), and dislodgement (2.2 events/1000 line days). Median life of catheters was 54 days (IQR 24-140). Line lifetime did not vary by insertion service (p=0.33), vessel (p=0.82), or procedure type (new vs. exchanged, p=0.08). Younger age was associated with shorter line life (p=0.04). Reason for line removal included dislodgement (21%), infection (23%), occlusion (21%), line breaks/malfunction (31%), and other reasons (5%). On multinomial regression adjusting for age and procedure type (new vs. exchanged), dislodgement was associated with newly placed lines (RR 6.9, 95% CI 2.2–21.7). Dislodgement was the cause for removal in 45% of new lines but 11.5% of exchanged lines. Accounting for procedure type and cause of removal, age was not independently associated with catheter life (p=0.16).

Conclusion: Pediatric IF patients depend on tunneled central venous catheters which have frequent complications. In this cohort, dislodgement of catheter was an unexpectedly common contributor to complications and loss of access, particularly in newly placed lines. Opportunities for simple interventions, such as closer attention to securing sutures and dressing application, should be investigated to mitigate these preventable complications.
ABSTRACT

Isolating Mammalian Plasma Membranes by Physical Disruption of Cells

KRISTINE MCANDREWS  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Levental Lab, NIH NIDDK

Keywords:  Plasma membrane model, plasma membrane isolation, lipidomics, lipid rafts, Giant Plasma Membrane Vesicle, GPMV, MDCK, HEK, Madin-Darby Canine Kidney, Human Embryonic Kidney 293T, plasma membrane patch.

Lipid rafts are organizing platforms within biological membranes that have been implicated in many physiological processes, including cell signaling and intracellular trafficking. Models of cellular plasma membrane (PM) are used to understand lipid rafts by studying membrane biophysical properties, like liquid-liquid phase separation. Giant plasma membrane vesicles (GPMVs) are isolated cellular PMs that maintain the native lipid and protein composition of the PM, in contrast to previously used synthetic models that contain only a limited set of components. GPMVs are made by chemically shocking mammalian cells, resulting in the loss of membrane asymmetry and an assembled cytoskeleton, two features that may be important in determining the physiological state of the plasma membrane and its organization (i.e. lipid rafts). With these caveats in mind, the objective of our project was to develop a PM model that more closely resembles the native physiological state of living cell membranes. We hypothesized that if physical, rather than chemical, disruption is used to isolate patches of cellular PMs, a model retaining native asymmetry and assembled cytoskeleton would result. Initially, we attempted cell disruption via hypo-osmotic shock, by applying water to adherent cells. The results from this procedure were unreliable and unreproducible, often resulting in large contaminations of intact whole cells along with areas of isolated PM patches. Instead, more consistent results (>90% by area cell-free PM patches) were found by freezing Madin-Darby Canine Kidney (MDCK) or Human Embryonic Kidney 293T (HEK) cells in water, thawing, and washing away cellular contents not attached to the plate. Immunofluorescence showed successful removal of nuclei and lysosomes, although some residual endoplasmic reticulum (ER) and golgi apparatus membrane remained. Western blotting was performed to quantify the purity of the preparations. An increase in the PM marker protein relative to total protein was observed, but an increase in ER marker protein was also observed. Future work will include using the patches for microscopic characterization of membrane physical behaviors, and optimization of patch production for PM isolation and lipidomics.
ABSTRACT
Degree of Cirrhosis Influences Survival Following Transarterial Chemoembolization for the Treatment of Unresectable Hepatocellular Carcinoma

KATHERINE MCELROY  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Dr. Curtis J. Wray, MD, General Surgery, Surgical Oncology
Supported by:  Dr. Curtis J. Wray, MD
Key Words:  Hepatocellular carcinoma, transarterial chemoembolization, cirrhosis

Background: Data regarding transarterial chemoembolization (TACE) as a treatment for unresectable hepatocellular carcinoma (HCC) in the context of extensive cirrhosis is ambiguous. Following TACE, 10-20% of patients studied experienced hepatic decompensation. As of now, little evidence delineates circumstances in which TACE would be an unsuitable therapeutic modality.

Objective: Our experiment analyzes whether TACE operation within our institution has greater beneficial outcomes compared to best supportive care (BSC) or systemic therapy for unresectable HCC with cirrhosis.

Methods: Data of institutional HCC cases treated with TACE (Doxorubicin eluting beads), chemotherapy, or BSC was compiled including standard demographic variables. Patients treated with surgery or ablation were excluded from this study. Post-2008, the data contained a multidisciplinary tumor board (surgical oncology and interventional radiology) coded as a binary variable. Using age, stage, gender, alpha-fetoproteins, albumin, MELD score at diagnosis and time period, inverse probability of treatment weighted propensity scores were created. These scores were included in a Cox proportional hazards model to estimate survival. In addition, variables associated with survival less than 90 days (S<90D) were identified via a logistic regression model.

Results: 746 HCC patients were included in this study. Treatment included: TACE only 141 patients (19%), chemotherapy only 135 (18%), BSC 415 (56%) and both 55 (7%). The percentage of patients receiving TACE tripled (12% to 33%, p<.05) after utilization of the tumor board in 2008. TACE increased mean survival an additional 9.9 months (95%CI:0.82-18.9, p<0.05) from an estimated mean survival of 12.0 months (95%CI:9.83-14.2, p<0.05) of patients treated with either chemotherapy or BSC. For patients treated with TACE, variables associated with S<90D included MELD (OR 1.16, 95%CI:1.04-1.29, p<0.01) and stage III (OR 12.1, 95%CI:1.40-16.3, p<0.03). Stage I&II patients receiving TACE had a greater than 50% probability of survival more than 90 days if they also had a MELD score of less than 22. Stage III HCC patients receiving TACE only had a similar survival benefit if their MELD score was less than 15.
Conclusions: Compared to chemotherapy or BSC, locoregional TACE significantly improved survival in HCC patients with cirrhosis. With increasing MELD scores, especially above 15, benefit of TACE diminishes for unresectable HCC.
ABSTRACT

The Oncometabolite D-2-Hydroxyglutarate Activates Autophagy in Myocytes

DANIEL MCNAVISH

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Sponsored by: Heinrich Taegtmeyer, MD, DPhil Department of Internal Medicine
Supported by: Heinrich Taegtmeyer, MD, Department of Internal Medicine, The University of Texas at Houston Medical School – Office of the Dean
Key Words: D2-HG, metabolism, oncometabolite, autophagy, LC3, AMPK, mTOR

Background: About 20% of acute myeloid leukemias (AMLs) harbor mutations of isocitrate dehydrogenase (IDH) 1 and 2, which reduce α-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxyglutarate (D2-HG). Elevated serum D2-HG levels in AML are accompanied by systemic effects including heart failure. It was recently shown that D2-HG impairs cardiac contractility by inhibiting the Krebs cycle enzyme α-Ketoglutarate dehydrogenase (α-KGDH), and causes heart as well as skeletal muscle atrophy. Therefore I am now proposing that D2-HG activates autophagy in myocytes.

Methods: I used L6 myocytes (L6Ms, rat skeletal muscle cell line) as a model. Cells were grown to confluency and differentiated to myotubes using DMEM containing 1% penicillin/streptomycin and 5% Fetal bovine serum (FBS). Cells were treated in FBS-free culture medium for 24 h with or without D2-HG (1 mM). To assess autophagic flux, cells were cultured under the same conditions in presence of 0.1 μM Bafilomycin A1 (BafA1) and subjected to immunoblotting. Nucleoporin 62 (p62) shuttles ubiquinated proteins to the autophagosome, thereby facilitating the clearance of ubiquitinated proteins. I determined the protein expression of p62 at 2, 4, and 6 hours in response to D2-HG. I further measured gene expression of the muscle-specific ubiquitin E3-ligases atrophy gene-1/muscle atrophy F-box (Atrogin-1/MAFbx) and muscle ring-finger protein 1 (MuRF1) and genes encoding for proteins regulating autophagy (e.g. Beclin1, p62) using qRT-PCR.

Results: D2-HG increased the conjugation of microtubule-associated protein 1A/1B-light chain 3 to phosphatidylethanolamine (LC3-II) in differentiated L6 myocytes within 24 h, which is consistent with increased recruitment of LC3 to autophagosomal membranes. In presence of the lysosomal inhibitor BafA1, D2-HG-treated cells showed increased expression of LC3-II, which is consistent with increased autophagic flux. I further observed increased phosphorylation and activation of AMPK, while mTOR and Akt phosphorylation was decreased. D2-HG reduces the intracellular ATP/AMP ratio which in turn activates AMPK and inhibits mTORC1, resulting in stimulation of autophagy and inhibition of protein synthesis by intersecting pathways. At the same time, I observed that the expression of p62 decreased 4 h after addition of D2-HG and returned back to control levels after 6 h. Binding of the autophagosome to the lysosome causes degradation of p62 as observed in my experiments. Gene expression of Atrogin-1/MAFbx and MuRF1 was unchanged, while BECN1 (Beclin1) as well as LC3 started increasing 6 h after addition of D2-HG and stayed significantly elevated after 16 h. My data indicates that addition of D2-HG increases the gene expression of proteins regulating autophagy.
Conclusion: D2-HG promotes autophagy activation through post-translational and transcriptional mechanisms.
Inter- and Intra-observer Variability in Assessment of Femoral Head Alpha-Angle: A Comparison Between CT and MRI 3D Modeling

RAMZY MEREMIKWU  McGovern Medical School at UTHouston  Class of 2020

Sponsored by:  Nicholas Beckmann, MD, Department of Diagnostic Imaging, Derek West, MD, Department of Interventional Radiology

Supported by:  Summer Research Project; Nicholas Beckmann, MD, Derek West, MD

Key Words:  Femoral Head, Alpha Angle, Inter-Intra Observer, 3D MRI, 3D CT

Femoroacetabular impingement (FAI) is a common cause of anterior hip pain. FAI can be caused by over-coverage by the acetabulum (pincer-type FAI) or by abnormal morphology of the anterosuperior femoral head (CAM-type FAI). In young adult and pediatric patients, the CAM-type of FAI predominates. When the CAM-deformity of the femoral head is severe, resection of a portion of the femoral head may be required to relieve the impingement. Accurate assessment of the CAM-deformity on preoperative imaging can be useful for planning. Preoperative assessment of CAM-deformities involves subjective assessment by the surgeon as well as objective assessment by measuring the alpha-angle. The alpha angle” is an angular measurement that helps quantify the severity of the CAM-deformity. Larger CAM-deformities are associated with larger alpha-angles.

3D CT has been the gold standard for preoperative assessment of CAM-deformities due to its superior depiction of the deformity compared with 2D CT and radiography. More recently, studies have been performed to demonstrate 2D MRI capability to diagnosis CAM-deformities. Utilization of MRI is preferred to CT because MRI spares patients from exposure to ionizing radiation. In addition, MRI has the ability to characterize labral tears and chondromalacia, two pathologies commonly associated with CAM-deformities that influence surgical management. However, MRI has not historically been capable of performing 3D modelling of the bone. Depending on plane of imaging, MRI of CAM-deformities suffers the same limitation of variability in alpha angle that is seen in 2D CT imaging. To date, there have been few studies using 3D MRI modelling of the femoral head to assess CAM-deformities, and there is no commercially available software to perform 3D MRI modelling.

This study aims to demonstrate that the interobserver variability of alpha-angle measurement using 3D MRI modelling is comparable to 3D CT modelling. We believe the images are comparable. The observers will be a rising 2nd year medical student and accredited board-certified musculoskeletal Radiologist. Results showed that the alpha-angle degree differences between 3D CT and 3D MRI were not clinically significant with a 95% confidence interval. Compared to 3D CT modeling, MRI exhibited statistically significant resolution and bone modeling, with a P value < 0.05. An interobserver correlation coefficient (ICC) was calculated to determine the amount of agreement between the two observers. ICC values were designated as Poor-Fair-Good-Excellent with 80% of ICC values rating as Fair (Fair = ICC from 0.4 - 0.59). 3D CT is the gold standard for FAI-CAM, but 3D MRIs can offer a great alternative when patients may also suffer from radiation sensitivity, associated labial tears, or chrondromalacia along with their FAI-CAM diagnosis.
ABSTRACT

Pain Management Following Primary Palatoplasty:
Improving Transition of Care

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Class of 2020

Sponsored by: Matthew R. Greives, MD, Department of Pediatric Surgery
Key Words: Pain Management Following Palatoplasty

Background: Post-operative pain following palatoplasty may cause feeding and swallowing difficulty. Dedicated pediatric pain service teams provide consistent, controlled pain management during the inpatient phase of recovery. Proper pain management following transition from inpatient stay to outpatient status is important to prevent readmission and emergency department visits for pain. Our study focused on improving outpatient pain management and patient satisfaction by improving transition protocols for patients following primary palatoplasty.

Methods: An IRB approved retrospective analysis was performed for 56 patients undergoing primary palatoplasty. Data was obtained for length of stay, pain scale scores, inpatient narcotic dosages, and inpatient readmissions/emergency department visits. Separately, an IRB approved prospective trial of 27 patients who underwent primary palatoplasty was also performed. Patients were identified and consented during their preoperative clinic visit. Following surgery, patients were assessed for the same metrics as the retrospective cohort. Prior to discharge, parents were required to fill narcotic prescriptions. The pediatric pain service team focused on teaching parents improved pain management strategies like augmenting narcotic medications with non-narcotic medications. Parents also received a narcotic usage chart to record the outpatient narcotic dosages per day. Parents reported results to the surgeon during a two-week follow-up visit and participated in a five-point satisfaction survey (1=very unsatisfied, 5=very satisfied).

Results: Data was obtained retrospectively for 56 patients and prospectively for 27 patients who underwent primary palatoplasty. No significant difference was observed for length of stay, pain scale scores, or inpatient narcotic dosages per day. These results demonstrate consistent inpatient pain management between the cohorts. Outpatient medication logs were completed for 9 (33%) patients showing a continued decrease in narcotic usage at home with no spike post discharge day 1. Patient satisfaction surveys were completed by 12 (44%) parents and showed high satisfaction levels for inpatient pain management (4.66 ± 0.49) and even higher satisfaction levels for comprehension (5.0 ± 0) and management of pain (4.92 ± 0.29) at home. Inpatient readmission/emergency department visits for palatoplasty decreased from 10.7% (6) following the previous protocol to 0% with the new transition protocol (p=0.079).

Conclusion: Pediatric pain service teams provide excellent inpatient pain management following primary palatoplasty. Proper transition from inpatient to outpatient can be achieved through parent education of pain management strategies and filling narcotic pain prescriptions prior to discharge. This transition protocol improves parent and patient satisfaction.
ABSTRACT
Re-evaluation of Team Based Learning sessions in Systems-Based Curriculum

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Supported by:  McGovern Medical School Curriculum committee
Key Words:  team based learning, medical school curriculum, systems based curriculum

BACKGROUND
Team-based learning (TBL) was introduced to McGovern Medical School as an instructional method in the new systems-based curriculum in 2016. There were 19 TBL cases in total, presented on a weekly basis over the span of the first semester. The TBL cases were designed to introduce problem solving sessions in a collaborative group environment, building upon the topics discussed through lecture content presented each week.

SIGNIFICANCE
An evaluation was administered to the pilot first year class after they had completed all TBLs to gain a clearer idea of their TBL experience. The strengths and weaknesses of the TBL system were gathered from this data and used in this project to improve the subsequent TBL sessions.

METHODS
An outline of the ideal TBL case was designed, and a rating system was created to highlight what factors of TBL were most important to the learning process. The following factors were evaluated for each case and given a rating based on the quality: the case introduction lecture (2 pts), the pre-reading assignment (1pt), and the TBL case exercises (2pts). Each TBL was given a rating out of 5, which helped gauge the level of improvement necessary for each case. This also helped highlight which cases were the most ideal and could later serve as a model for the ones rated more poorly. Cases were also evaluated based on how well they integrated with that week’s lecture topics and how appropriate they seemed for the level of first year medical students, with reference to the learning objectives covered by the guidelines for the USMLE Step 1 exam.

RESULTS
Each case was reviewed carefully and a list of changes to be made were discussed with the appropriate faculty responsible for each case. The changes were implemented and the current class of first year students are attending the new sessions. Data from the new class will be gathered in October 2017.

CONCLUSIONS
Although data has not yet been collected from the current class, it is believed that improvement of TBL sessions will greatly increase student understanding of the topics covered and provide an overall benefit to student learning.
ABSTRACT

Blood Product Utilization after Acute Non-Compressible Hemorrhage below the Diaphragm: Evaluation of the Impact of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) on Emergent Blood Product Use

MEGAN MONT
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Sponsored by: Laura J. Moore, M.D., John Harvin, M.D., Charles E. Wade, PhD
Supported by: McGovern Medical School Department of Surgery; CeTIR
Key Words: REBOA, non-compressible hemorrhage, blood product

Background: Noncompressible hemorrhage is a leading cause of death in trauma patients. Aortic occlusion (AO) is a potentially life-saving adjunct in the resuscitation of hemorrhagic shock patients and can be performed via resuscitative thoracotomy, exploratory laparotomy, or Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) [1-3]. In patients suffering from hemorrhagic shock, temporary AO via REBOA may offer the advantage of decreasing the amount of blood product required while awaiting definitive hemorrhage control by supporting cardiac/cerebral perfusion and diminishing aortic inflow to the area of injury. We hypothesized that patients that undergo REBOA with balloon inflation at Zone 1 (thoracic aorta) will require fewer blood products during the first 24 hours as compared to case matched controls that do not undergo REBOA.

Methods: We conducted a propensity score matching analysis of trauma patients undergoing emergent laparotomy from October 2011 to July 2017 at the Red Duke Trauma Institute. Patients who received REBOA were matched to those who did not based upon their propensity scores, which were determined based upon the following variables: year of operation, attending surgeon, age, gender, mechanism of injury, arrival physiology, arrival coagulation profile, focused abdominal sonography for trauma results, and injury severity via injury severity score (ISS) and abbreviated injury scores (AIS). Our primary outcome was units of red blood cells (RBC) transfused during laparotomy.

Results: During the study period, 1,263 patients underwent emergent laparotomy and 61 (5%) of these patients also underwent preoperative Zone 1 REBOA. Based upon propensity scores, 37 REBOA patients were matched to 37 non-REBOA patients. The matching appeared adequate as the propensity scores, demographics, injury severity, and arrival physiology were similar between the two groups. A comparison of the results is presented in Table 1. The median intra-operative RBC transfused was significantly higher in the REBOA group (median 12 units IQR [6, 22] vs 6 units IQR [1, 12], p=0.006). Upon closer inspection, the REBOA group did not appear to be a similar group to the non-REBOA group. The REBOA group had a higher rate of estimated blood loss (median 2,250 cc IQR [550, 4,750 versus 900 cc IQR [250, 2,250], p=0.097), damage control laparotomy (51% vs 38%), deaths due to hemorrhage (46% vs 21%), and intra-operative deaths (29% vs 8%). The REBOA group also had a lower rate of definitive laparotomy (19% vs 54%) and a higher number of deaths due to traumatic brain injury (36% vs 19%).

Conclusion: In this study, we aim to use the largest observational dataset available in the United States to determine the treatment effect of REBOA on intra-operative RBC transfusions. While the two groups appear similar in terms of propensity scores, demographics, injury severity, and arrival physiology, there appear to be confounding factors that are not accounted for in the analysis, such as patient selection for REBOA and the trauma surgeon’s clinical identification of patients’ severity of injury. The only manner to account for these potential confounding factors is randomization and a prospective, randomized controlled trial is necessary to obtain an accurate treatment effect of REBOA.
<table>
<thead>
<tr>
<th>Variable</th>
<th>No REBOA (n = 37)</th>
<th>REBOA (n = 37)</th>
<th>p value</th>
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<td>Head AIS</td>
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<td>82 (67,107)</td>
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<td>85 (72,105)</td>
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<td>First OR pH</td>
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<td>7.14 (7.05, 7.23)</td>
<td>0.028</td>
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<td>7.5 (4.9, 10.1)</td>
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</tr>
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<td>First OR Base Excess</td>
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<td>-10 (-15, -6)</td>
<td>0.056</td>
</tr>
<tr>
<td>OR RBC transfusion</td>
<td>6 (1, 12)</td>
<td>12 (6, 22)</td>
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<tr>
<td>OR FFP transfusion</td>
<td>6 (0, 12)</td>
<td>10 (5, 22)</td>
<td>0.052</td>
</tr>
<tr>
<td>OR platelet transfusion</td>
<td>6 (0, 12)</td>
<td>12 (6, 18)</td>
<td>0.042</td>
</tr>
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<td>OR EBL</td>
<td>900 (250, 2250)</td>
<td>2250 (550, 4750)</td>
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<td>Mortality</td>
<td>14 (37%)</td>
<td>27 (73%)</td>
<td>0.002</td>
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</table>

Table 1.1

References
ABSTRACT

Does Surveillance Bias Impact the Incidence of Deep Venous Thrombosis and Pulmonary Embolism at US Trauma Centers?

VICTORIA MORRIS  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Bryan A. Cotton, M.D., M.P.H., F.A.C.S., Department of Surgery

Supported by:  CeTIR and McGovern Medical School Dean’s Office

Key Words:  DVT, PE, Trauma, Screening

Background and Significance:
Venous Thromboembolism (VTE) is one of the most common complications of trauma patients and is a significant cause of mortality and morbidity¹. VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) and can affect up to 600,000 patients a year². In addition to third-party payers, many public and private agencies consider VTE incidence to be a marker for quality of care³. However, multiple studies have shown that rates may be affected by variability in screening practices, and that increased screening yields higher incidence⁴,⁵,⁶. We set out to evaluate the incidence of both DVT and PE at Memorial Hermann Hospital, considering current screening practices for VTE post-trauma.

Specific Aim: Evaluate Memorial Hermann Hospital’s DVT/PE rate and rate of screening tests order per patient.

Design and Methods: Retrospective cohort study, examining VTE events, screening Duplex ultrasound, and screening CT-angiograms (CTA) of the chest per patient. Highest level-trauma activations over the age of 15 years admitted between 1/1/2016 – 12/31/2016. Excluded those who died in the first 24 hours, those who were pregnant, and those with >20% TBSA burns.

Results: 1314 patients met inclusion; 37 (2.8%) with PE and 27 (2.1%) with DVT. 201 patients had a CTA and there was a total of 451 CTAs performed; 8.2% of CTAs were positive. The median number of CTAs in patients with PE was 2 (1, 3) versus 0 (0, 0) in those without PE; p<0.001. 95% of PE patients had at least one CTA versus 13% of those without PE, 80% of PE patients had at least two CTAs versus 11% of those without PE, and 30% of PE patients had at least three CTAs versus 3% of those without PE; all p<0.001. Of the 201 PE’s, 13% were main pulmonary, 36% were lobar, 24% were segmental, and 27% were subsegmental. 141 patients had a Duplex scan and there was a total of 190 Duplex scans performed. 14.2% of Duplex scans were positive. The median number of Duplexes in patients with DVT was 1 (1, 2) versus 0 (0, 0) in those without DVT; p=0.003. 85% of DVT patients had at least one Duplex versus 9% of those without DVT and 30% of DVT patients had at least two Duplexes versus 2% of those without DVT; both p<0.001. Controlling for age, male gender, and injury severity, the number of CTAs was independently associated with an OR of 2.6 for finding a PE, while the number of Duplex ultrasounds was associated with an OR of 4.6 for finding a DVT.

Conclusions: The rate of VTE events in trauma centers is dependent on the intensity of screening for these events. An adjustment should be made for intensity of screening for these significant events when assigning scores for hospital performance and for reimbursement, least government, insurance, and quality organization discourage physicians and their hospitals from searching for these morbid and sometimes fatal events.
Future Work: Validation of event rates at other US trauma centers.
Dermatological Disorders in ESRD Patients: Effect on Quality of Life

CRYSTAL NWANNUNU  
*McGovern Medical School at UTHealth*

**Background:** Patients on hemodialysis due to end stage renal disease (ESRD) have an increased risk and often present with disorders of the skin, nails and hair. Published research notes common cutaneous presentations in ESRD, but the presentation frequency in hemodialysis patients and its impact on patient quality of life (QOL) is less well understood.

**Hypotheses:** Dermatologic disorders in hemodialysis patients negatively impact patient QOL. Treatment for these dermatologic disorders can improve patient QOL and overall care.

**Methods:** A 20 question multiple choice survey was developed in consultation with a nephrologist. The survey consisted of a patient perspective outcome measure to elicit the types of prevalent disorders of the skin, nails and hair, impact on QOL and satisfaction of physician care toward the patient’s dermatologic conditions. The survey was verbally administered to 39 adult ESRD patients undergoing chronic in-center hemodialysis at Davita PDI North and Davita PDI South in Houston, Texas. The results were recorded in Qualtrics survey software. A regression analysis was preformed to assess association between dermatologic manifestations and QOL impact.

**Results:** Of the total participants, 33 (85%) presented with dermatological manifestations, with 31 (94%) experiencing skin disorders, 10 (30%) experiencing nail disorders, and 12 (36%) experiencing hair disorders. When asked if their cutaneous disorders negatively impacted QOL and if receiving treatment for their disorders could yield improvement, 24 (73%) and 18 (55%), respectively, gave affirmative responses. 24 (73%) participants were satisfied with their physician’s execution of care and concern for their dermatologic disorders. Regression analysis showed association between dermatologic disorders and negative impact on QOL in these hemodialysis patients.

**Conclusion:** Dermatological disorders experienced by ESRD dialysis patients negatively impact their QOL. One-fourth of ESRD dialysis patients were dissatisfied with their nephrologist’s care for their dermatologic disorders. When focused solely on one specific specialization, physicians can neglect the additional adverse effects patients experience increasing cognitive bias. Addressing the dialysis patient’s dermatologic concerns in addition to their routine dialysis treatment can steer current/future physician treatment practice towards a better holistic execution, improving patient QOL and satisfaction with their physician care.
ABSTRACT
Comparable Responses in Male and Female to Cerulein-Induced Pancreatic Injury and Recovery

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Sponsored by:  Tien C. Ko, MD, Yanna Cao, MD, Department of Surgery.
Supported by:  National Institute of Diabetes and Digestive and Kidney Diseases, 5T35DK007676-24
Key Words:  Chronic Pancreatitis, Cerulein, Male, Female

Introduction:  A higher incidence of chronic pancreatitis (CP) in males has been reported in human studies. Whether CP is reversible and whether sex factor influences CP recovery, remains unclear. Cerulein, a cholecystokinin analogue that induces CP, is a commonly used and replicable CP mouse model. Using the cerulein CP model for a simulated period of CP injury and recovery, we tested our hypothesis that sex-dependent differences would occur during CP injury and recovery. Methods:  Adult C57BL/6 mice were administered cerulein (n=3-6/sex/group, 50µg/kg, 5x hourly/day, 3 days/week, ip) for 4 weeks, then allowed a 4-week recovery period. Normal saline was injected as control. Body weight was recorded weekly. Pancreata were harvested, either 4 days (injury group) or 4 weeks (recovery group) after the last injection and weighed. Pancreatic paraffin sections were stained for hematoxylin and eosin, and parenchymal acinar injury was scored. Fibrosis was assessed by Sirius Red staining for extracellular collagen deposition. Macrophage infiltration was evaluated by CD68 immunohistochemistry. Results:  From week 3-4 and 2-6, male and female mice injected with cerulein weighed less than their time matched controls, respectively (p<0.05). Four days after CP induction in injury groups, compared to the control groups, pancreatic injury was shown (respective to males, females) by decreased pancreas weight/body weight ratio (-50, -55 %), increased acinar injury score (+3, +3), increased fibrosis (15, 11 % additional area/field), and increased macrophage infiltration (8, 23 additional cells/field). Both males and females displayed similar responses on acinar injury and fibrosis, while females exhibited a 3-fold greater macrophage infiltration than males (p<0.05). Four weeks after CP induction in recovery groups, pancreatic recovery occurred (respective to males, females) with a recovery of pancreas weight/body weight ratio (29, 33 %) and reversal of acinar injury (95, 100 %) and fibrosis (61, 45 %). Similar recovery responses for these parameters were observed in both males and females. A full reversal of macrophage infiltration was observed in females and males. Notably, the time-matched control for the recovery mice, possessed higher baselines of macrophage infiltration than CP injury group. Conclusion:  Male and female mice gained less body weight with induction of cerulein, but both showed recovery to normal weight after withdrawal of insult. Cerulein-induced acinar injury is reversible, while fibrosis is partially reversible. Both male and female mice demonstrate comparable responses in CP injury and recovery, except for macrophage infiltration. Time-matched groups should be used in animal design models for CP,
to account for potential aging factors, as the control group, possessed higher baseline infiltration than the CP injury group.
ABSTRACT
The Clinical Spectrum of Patients with a Novel Heterozygous p.G366A Mutation in POLG1

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Sponsored by:  Mary Kay Koenig, M.D. & Rahmat Adejumo, MBBS., MPH
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Key Words:  mitochondrial disorder, POLG1, pol-γ, depletion syndrome

Background:  The electron transport chain is the essential cellular process for performing oxidative phosphorylation of ADP to ATP (Lamperti & Zeviani, 2016). Mitochondrial disorders are a group of clinical diseases that result from defects in the mitochondrial electron transport chain. The inheritance pattern of mitochondrial disorders can be autosomal dominant, autosomal recessive, x-linked, or maternal with mutations occurring either in the nuclear or mitochondrial DNA (Hudson & Chinnery, 2006). POLG1 is a nuclear gene encoding the catalytic subunit of the mitochondrial polymerase gamma (pol-γ). POLG1 is the only enzyme known to replicate mitochondrial DNA in humans and is one of the most commonly mutated genes affecting mitochondrial function (Di Fonzo et al., 2003). POLG1 mutations prevent proper proofreading during mitochondrial DNA replication and, over time, patients develop a depletion of their mitochondrial DNA producing increasing numbers of non-functional mitochondria. Disease is inherited via either autosomal dominant or autosomal recessive changes. The clinical spectrum varies greatly both between and within families (Tang et al., 2011). Herein, we describe the clinical presentation of a family carrying a novel heterozygous POLG1 mutation (c.1097G>C; p.G366A).

Methods:  We performed a phenotype-genotype study, using patients from the University of Texas Mitochondrial Center of Excellence. Patients with the c.1097G>C (p.G366A) mutation in POLG1 were included (HSC-MS-09-0057).

Results:  A total of four patients within the same family were identified with the c.1097G>C (p.G366A) mutation in POLG1. A muscle biopsy from the mother illustrated decreased levels of mitochondrial DNA (29% of control), confirming the diagnosis of a depletion syndrome. The mother had mild cognitive impairment. Other symptoms onset in her mid-30s, including diabetes mellitus, chronic constipation, gastric neuropathy, gastro-esophageal reflux disease, hypertension, and migraine headaches. Her two sons are also cognitively impaired and have symptoms of congenital heart defects, dysphagia, seizures, myoclonus, and tremors. Her daughter developed symptoms at age 7 years, initially presenting with muscle spasms and weakness in her lower extremities. In her early-20’s she is now pre-diabetic.

Conclusion:  The genotype-phenotype correlation of POLG1 mutations is poorly understood. Dominant mutations appear to produce a milder phenotype however symptoms vary greatly in severity and age of onset. We presented here a family of four carrying a novel POLG1 mutation [c.1097G>C (p.G366A)] producing a mitochondrial depletion syndrome. The most common clinical symptoms noted in our patient pool were cognitive impairment, seizures, gastrointestinal dysfunction, diabetes mellitus, and myopathy.
ABSTRACT

Localizing Refractory Pediatric Epilepsy using Resting State MRI

LUDOVIC PAO

Sponsored by: Manish N. Shah, MD, Pediatric Neurosurgery
Supported by: Manish N. Shah
Key Words: Epilepsy, Localization, Resting State MRI

Epileptic seizure foci have been shown to affect resting state brain networks. This novel retrospective study aims to correlate resting state functional MRI (rsMRI) signal latency with pediatric epileptogenic foci lateralization.

rsMRI and anatomical MRI scans were obtained from 80 prospectively registered epilepsy patients and 585 control patients from the ADHD 200 data set. The MRI scans were preprocessed and registered using standard rsMRI techniques. Latency maps were generated by voxel-wise maximal cross-covariance parabolic interpolation of rsMRI signal lag and the global signal. Statistical maps were created for each epilepsy patient using control mean and standard deviation maps. By applying z-value thresholds to statistical maps, two-tailed hypothesis testing was performed. Threshold values were obtained via uncorrected thresholds (α=0.05, 0.01, 0.005, 0.001), false discovery rate (FDR, Benjamini-Hochberg, q=0.05) and family-wise error rate (FWER, Bonferroni, α=0.05) methods, the former two correcting for multiple comparisons. Significantly latent areas were counted for right and left hemispheres. The hemisphere with more latent areas was predicted to contain the seizure foci. To determine prediction accuracy, postoperative imaging was examined for procedure type and lateral side.

A greater than 50% prediction rate in all but one test was observed (FDR for Lesion/Lobectomy=50%). A 100% prediction rate was observed for the most specific test per procedure. Some latent areas were local to seizure foci when qualitatively examined alongside postop images.

rsMRI temporal latency analysis has shown promise in lateralizing and localizing seizure foci. Additional prospective, multicenter studies will further characterize the relationship between signal latency and epileptogenic foci.
ABSTRACT

Abnormal Routine Preoperative Laboratory Tests in Outpatients’ Endoscopies at MD Anderson Cancer Center

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Sponsored by: Linh T. Nguyen, MD, Department of Anesthesiology and Perioperative Medicine

Supported by: Linh T. Nguyen, MD

Key Words: Endoscopy, anesthesia, gastroenterology

BACKGROUND: Laboratory tests are conducted perioperatively often as a means of assessing the safety of a procedure for a patient and predicting possible adverse outcomes. Lab tests are classified as routine if they have no specific purpose, or indicated if for a specific clinical purpose. At MD Anderson Cancer center, the patient population generally has a more significant medical history. Outpatients undergoing endoscopies under anesthesia may be more likely to have abnormal lab results that may lead to adverse outcomes compared to outpatients at other general practices. Therefore, the Anesthesia Assessment Center at MD Anderson orders routine lab tests including electrolytes, BUN, creatinine, complete blood count, and thyroid panels for all outpatients scheduled for an endoscopy under general anesthesia. This study aims to examine the frequency of abnormal routine lab tests and evaluate their predictive value for adverse perioperative events in outpatient endoscopies under general anesthesia at a tertiary cancer center. We hypothesize that the routine preoperative labs are not necessary for a safe anesthetic in patients undergoing outpatient endoscopies under general anesthesia, and eliminating them can result in cost savings.

METHODS: This retrospective study includes all adult (18 years and above) outpatients with endoscopic procedures under general anesthesia at MD Anderson Cancer Center from June 16th, 2015 until January 15th, 2017. The procedures included in this study are esophagogastroduodenoscopy (EGD), colonoscopy, percutaneous endoscopic gastrostomy (PEG), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). Lab results within 1 month prior to the patients’ procedure will be retrieved from ClinicStation and Epic EMRs. The following data was gathered if present within 2 weeks after the procedure: cancelled procedures, post-procedural complications, cardiology, neurology, or pulmonology consultations, hospital admissions, emergency center visits, chest X-Rays, cardiac markers, and MRI or CT of the brain. Additionally, deaths within 1 month following the procedure were also gathered.

ANALYSIS: Descriptive statistics will be used to analyze the patients’ demographic data alongside the lab values and post-operative outcomes. Students t-Test will be used for continuous variables, and the chi-squared test for comparing the categorical values. The sensitivity, specificity, and positive predictive value (PPV) will be estimated for each abnormal lab value in determining adverse perioperative events.
ABSTRACT
Assessing the Use of Fecal Microbiota Therapy in the Treatment of Multidrug-Resistant Enterobacteriaceae

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Sponsored by: Dr. Herbert Dupont, MD, & Dr. Zhi-Dong Jiang, Ph.D, University of Texas School of Public Health
Supported by: NIH-NIDDK grant
Key Words: Multidrug resistance, extended-spectrum beta-lactamase, fecal microbiota therapy

Fecal Microbiota Transplant (FMT) is a novel approach to eliminating antibiotic-resistant Enterobacteriaceae in patients harboring multi-drug-resistant microbiota. It is hypothesized that FMT therapy markedly reduces abundance of multi-drug resistant bacteria such as extended-spectrum-beta-lactamase E.coli (ESBL) and/or vancomycin-resistant Enterococcus (VRE) in the gut microbiological compositions of patients with recurrent infection of Clostridium difficile (rCDI) with significant dysbiosis. A retrospective study on 136 subjects diagnosed with rCDI and treated with FMT was conducted to evaluate the efficacy of FMT in the eradication of invasive microbiota. 22 samples were positive for extended-spectrum beta lactamase resistance at the initiation of FMT and 14 recovered from ESBL by the date of last collection (3 from 30 days for FMT-1 and 11 from 90 days after FMT-2) (3 lost to follow-up). Out of 71 samples that were positive for VRE at the time of initiation of FMT, 37 of the patients resolved by the last sample collected (9 at 30 days for FMT-1 and 28 at 30 days for FMT-2) and 8 were lost to follow-up. The efficacy of FMT on a portion of the patients warrants further study into the use of this therapy to successfully treat individuals with recurrent multi-drug-resistant infection.
ABSTRACT

DIEP flap breast reconstruction performed at a small, community based safety-net hospital, with comparison of outcomes to the American Society of Plastic Surgeons Tracking Operations and Outcomes for Plastic Surgeons programs.

SNEHA PATEL

Sponsored by: Daniel J. Freet, M.D., Department of Plastic & Reconstructive Surgery
Supported by: Department of Surgery, Dean’s Office stipend
Key Words: Breast reconstruction, DIEP flap

Deep Inferior Epigastric Perforator (DIEP) flap breast reconstruction is an improved method of autologous tissue breast reconstruction with reduced insult to the abdominal wall, but at the same time requiring increased technical skill. This study summarizes the peri- and post-operative data collected on 64 patients that have undergone DIEP flap breast reconstruction. In our patient population, 6.25% experienced total flap loss, 3.13% experienced partial flap loss, and 0% experienced complications such as pulmonary emboli, septic shock, urinary tract infection, surgical site infection, myocardial infarction, cardiac arrest, stroke, coma, and death. This compares to a total flap loss rate of 2.71% and a partial flap loss rate of 1.51% in the American Society of Plastic Surgeons Tracking Operations and Outcomes for Plastic Surgeons (ASPS TOPS) data base over the last 5 years. Rates for our other peri-operative complications were all below or equal to those recorded in the TOPS database. Higher rates of total and partial flap loss at LBJ we suspect is due to resident physicians who have not mastered the fine art of microsurgery performing the vascular anastomoses. In addition, recognition of vascular compromise could be slower than necessary to revascularize and save the flap. We believe that with more education and training, DIEP flap surgeries could be safely offered to a wider patient population at LBJ Hospital in the near future.
ABSTRACT

An Investigation into the Mechanical Properties of Articular Cartilage

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Sponsored by:  Catherine G Ambrose, Ph.D., Department of Orthopaedic Surgery
Supported by:  NIH/NIDDK Grant, #2T35 DK007676-24
Key Words:  Mechanical Properties, biomechanics, articular cartilage, tissue engineering

Current orthopedic clinical practice for osteoarthritis attempts to relieve pain, aid repair, or delay damage using non-steroidal anti-inflammatory drugs, steroid injections, or hyaluronic acid injections. Following these palliative actions the clinician’s main recourse is synthetic total joint replacement. However, we are entering a new era where a biological, tissue engineered replacement is becoming feasible. There are several different methods used by researchers to test articular cartilage, but these methods vary widely and have not been standardized to ensure comparable results. In this study, we sought to standardize these by providing an outline for efficient articular cartilage testing that is easily repeatable. Crucially, these experiments lay the groundwork to establish standard testing methods for tissue-engineered cartilage prior to implantation. Testing these mechanical properties in first bovine, and then across human tissue samples, allows us to create a standard with which to compare future tissue engineered constructs.

The data obtained from the bovine mechanical testing can be used to compare to both other types of cartilage as a standard of the values that healthy cartilage should have, as there is a high degree of similarity between bovine and human articular cartilage mechanical properties. We tested these samples under various conditions, such as exposure to collagenases for different amounts of time to change their collagen content, levels of which can be assessed biochemically and histologically. We tested their compression and viscoelastic properties, as these have the most relevance to in vivo stress using compressive stress relaxation. These tests were run on an Instron 5848 using a 100N load cell and an unheated water bath with Phosphate Buffered Saline for the stress relaxation test. The cartilage was isolated with a diamond-coated drill bit with a 7/16” diameter and equilibrated with a vibratome to ensure even thickness. We applied compressive strains of 5, 10, 15, and 20% for 20 minutes each to assess the stress strain curves. This gave us a range of values for various content percentages of the collagen matrix proteins and the respective change on the mechanical properties of the underlying cartilage. Our data showed clearly that exposure to collagenase, even for short periods of time, caused significant structural changes and differences in the mechanical properties. The slope of the asymptotes of the stress-strain curve produced under these settings was different than that of untreated cartilage, and the difference was correlated with time of exposure. These results indicate a standard of testing that may be easily repeated in future testing of human articular cartilage as well as tissue engineered constructs.
Abstract

Pregnancy shows beneficial effects on dystrophic mice

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Sponsored by: Aiping Lu, MD, Department of Orthopedic Surgery
Supported by: Aiping Lu, MD
Key Words: DMD, dKO-heterozygous, MDX, pregnant, multi P

Introduction: Duchenne Muscular Dystrophy (DMD) is a genetic disorder characterized by the complete loss of dystrophin [1]. It currently has no cure despite the continued understanding of the disorder. It was previously shown by our lab that pregnancy improves the myogenic differentiation of myogenic progenitor cells (MPCs) in vitro and improves muscle regeneration in wild type (WT) mice in vivo. In this study, the effects of pregnancy were observed in MDX mice, which is a mouse model for DMD. To rule out hormonal effects present during pregnancy, dKO-heterozygous (dystrophin-/-/utrophin+/-) mice, which is another mouse model for DMD, that were previously pregnant up to five times (multi P) in the past were compared to virgin mice. Muscle histopathology was performed to compare the mice. Our results suggest that pregnant MDX mice and that previously pregnant dKO-heterozygous mice had overall better outcomes when compared to their controls. The results show that pregnancy has beneficial effects for dystrophic mice and that changes in the dystrophic microenvironment could be an approach to improve muscle weakness, despite the lack of dystrophin expression.

Methods: Animals: MDX pregnant mice that were pregnant (gestational age between 10-18 days) and non-pregnant mice of the same age were sacrificed. Multi P and virgin dKO-heterozygous mice of the same age were sacrificed. The gastrocnemius muscle was isolated, frozen, and sectioned.

Histochemistry: H&E and trichrome staining were performed. Trichrome was done to observe collagen deposition levels to assess the amount of fibrosis present.

Immunohistocytochemistry: Sections of muscle were fixed with 5% formalin. Mouse IgG, embryonic myosin heavy chain (e-MyHC), and F4/80 were used as markers with the Vector® M.O.M.™ immunodetection kit. Mouse IgG was used to observe muscle fiber necrosis. Newly regenerated myofibers were observed with e-MyHC. F4/80 was used to evaluate macrophage infiltration.

Results: Decreased fibrosis in pregnant MDX mice: Through trichrome staining, less fibrosis was seen in pregnant MDX mice when compared to the virgin control, which indicates circulating factors present during pregnancy are responsible for the marked improvement (Fig. 1A, 1B).

Increased muscle regeneration and decreased inflammation in pregnant MDX mice: Through immunostaining with e-MyHC and F4/80, increased muscle regeneration and decreased macrophage infiltration were observed in pregnant MDX mice, respectively (Fig. 2). However, by staining with mouse IgG, we observed that the amount of necrotic fibers was not lower in pregnant MDX mice (data not shown). Increasing the number of mice is needed to confirm this.
**Better outcomes in multi P pregnant dKO-heterozygous mice:** The results showed that multi P dKO-heterozygous mice muscle had less fibrosis and a lower number of necrotic fibers compared to the virgin control (Fig. 3). These results help disprove hormonal effects being a factor.

**Discussion:** Current treatment methods for DMD do not lead to full recovery; therefore, new alternatives are continually being investigated. Little has been done to look into changing the muscle microenvironment in DMD patients as a therapeutic approach. Parabiosis has been useful in revealing the ability of circulating factors in young mice to assist in muscle regeneration potential in older mice [2]. Pregnancy is a form of natural parabiosis and has shown to have a positive effect in WT mice with cardiotoxin injury [2]. The results of this study have shown that pregnancy also provides beneficial effects in the muscle of dystrophic mice. Additionally, during this study, dystrophic mice that were not pregnant, but had undergone multiple pregnancies in the past, were compared to virgin controls. The previously pregnant dystrophic mice had increased muscle regeneration. The results support the idea that hormonal effects were not the only reason for the better outcomes observed with pregnancy, but that presence of other circulating factors were upregulated due to pregnancy. DMD only affects males, but this study helps to prove a concept and develop a treatment for DMD patients. Future studies with increased sample sizes should be done to definitively determine if pregnancy assists in reducing the effects of muscular dystrophy disorders.

**Significance:** This study can lead to the development of novel and clinically relevant therapies for DMD patients.

**References:**
Outcomes of Enhanced Recovery After Surgery Protocols for Spinal Cancer Patients at MD Anderson Cancer Center

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Sponsored by: MD Anderson Cancer Center Department of Anesthesiology and Peri-op Med.
Supported by: Keyuri Popat, MD
Key Words: Enhanced Recovery After Surgery (ERAS), Enhanced Recovery for Spine Surgery (ERSS), cost, ICU, anesthesiology, surgery

Abstract

Introduction
There is already ample evidence showing that an Enhanced Recovery After Surgery program is effective in expediting patient recovery in various surgical specialties. Enhanced Recovery after Spinal Surgery (ERSS) for major spine surgery program was instituted at a tertiary cancer center. This program includes, but is not limited to, multimodal care involving nurses, dieticians, and physiotherapists alongside anesthesiologists and surgeons, adequate peri-op pain relief, early post-op ambulation, reduction in surgical stress, optimal intra-operative fluid therapy, and a change in anesthetic technique. Our hypothesis is that an ERSS approach would decrease ICU stay and thus ultimately reduce the cost burden.

Methods
A total of 220 major spinal surgical cases observed, 65 were non-ERSS cases (managed without the ERSS protocol) and 163 were ERSS cases (managed with ERSS protocol).

Results
The number of ICU admissions for open spine surgery were 16 out 163 in the ERSS group (9.8%) and 14 out 65 in the non ERSS group (21.5%) resulting in an 11.7% absolute reduction in post-surgical ICU admissions for open spine surgery.

Conclusion
At this tertiary cancer hospital, implementation of ERSS program has helped decreased the utilization of post-operative ICU care resulting in cost savings. A methodological review of ICU costs in the United States in 2010 estimated the cost per day in the ICU was $4,300, contrasting with a Healthcare Cost and Utilization Project (H-CUP) analysis stating that the average non-ICU cost per day for a cancer patient in 2009 was $3,300. With the implementation of the ERSS program, an estimated $1,000 per day of non-ICU admission per patient was saved.

References
ABSTRACT

Will flipping the classroom improve student satisfaction and student performance in the pre-clerkship curriculum?

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Sponsored by: Allison Ownby, Ph.D., ME.d., Educational Programs
Supported by: McGovern Medical School Summer Research Program in the Office of Educational Programs
Key Words: Medical Education, Flipped Classroom, Active Learning

Introduction: The “Flipped Classroom” (FC) is a model of instruction that allows students to engage in higher order thinking and more active learning in the lecture hall. In this model, a teacher assigns pre-class work and then engages in interactive activities in class that animates the pre-class assignments. This model is centered on the idea that class time is more effective when students are actively engaging with the material as opposed to passively receiving information from a teacher. There is evidence that active learning is more beneficial for student comprehension in science courses.1 To better understand whether the flipped classroom could benefit McGovern Medical students (MMS), Dr. Carpenter and I worked this summer to “flip” five of the standard biochemistry lectures from Block 1 of Foundations.

Methods: Data were collected by surveys via Qualtrics and Block 1 summative performance via ExamSoft. All data were collected anonymously and are reported in aggregate. There was a pre and post-test survey and a survey after the four flipped classroom sessions. The first-year medical students were asked to complete an anonymous two-question pre-test survey before their first flipped classroom session. This survey asked about the student’s perceptions of the flipped class model. Students then had to complete a 5-question survey at the end of each flipped class which asked about the effectiveness of the video and use of class time. Students were then asked to complete another two-question survey after the block 1 summative exam asking about their perception of the FC model again.

Results: The pre-test vs post-test survey indicates that students preferred the flipped classroom model as opposed to the traditional lecture. In the first survey, 6 students (19.35%) preferred a flipped classroom while 13 students (41.94%) preferred a traditional lecture. In the post-test survey 40 students (57.14%) preferred the flipped classroom as opposed to 16 students (22.86%) who preferred the traditional lecture. These two surveys indicate that students grew to prefer the FC model of learning as opposed to the traditional lecture. After the first flipped class, 111

students (46.64%) strongly agreed that class time was used effectively while 95 students (39.92%) somewhat agreed. In the second flipped class 118 students (69.82%) strongly agreed that the class time was used effectively while 36 students (21.30%) somewhat agreed. The last two after class surveys are still being interpreted. From the first two after class surveys, most students believed that the FC model was an effective use of their time. Summative examination data are still being analyzed, but from the preliminary paired t-test conducted, results suggest that while there was improvement in performance scores, differences were not significant.

Conclusion: From this study, students in the pre-clerkship curriculum at MMS believe the FC model of learning is effective and most students have grown to prefer this model. Research should be focused on expanding this model of learning to other classes in the pre-clerkship curriculum.
ABSTRACT

Impact of Smoking on Trauma Patients Expected to Receive Massive Blood Transfusion

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Sponsored by:  Charles E. Wade, PhD
Supported by:  Center for Translational Injury Research
Key Words:  Trauma, Smoking

Background: Thirteen percent of all Americans smoke and/or use tobacco products. This percentage is higher in the trauma population. The adverse long-term effects of smoking are well documented. The cardiovascular literature describes the phenomena of the “Smoker’s Paradox” where smokers who undergo acute myocardial infarctions (MI) have overall lower short-term mortality, though no difference or worse outcomes long term. The current literature is divided on the impact of smoking and tobacco use on the trauma population. We hypothesized that patients with severe traumatic injuries who smoke will have worse outcomes in terms of mortality, length of stay, and complications.

Methods: We conducted a retrospective analysis of patients who were enrolled in the PROPPR study. The PROPPR study was a multi-institutional study that looked at the effects on mortality and morbidity of two transfusion protocols in patients expected to receive massive blood transfusions. Patients were divided into two groups based on known tobacco use. Multivariate analysis for mortality was assessed for 24 hours and 30 days taking into account ISS score, blunt vs. penetrating, head AIS score, PROPPR treatment group, age, etc. In addition, cytokine data were analyzed.

Results: There were no differences in basic demographics (p> 0.05) between smokers (n=140) and non-smokers (n=540): median (IQR), Age= 35 (26, 49.5) vs 33.5 (24, 51), ISS= 24 (14, 34) vs 29 (18, 41), RTS= 6.90 (5.03, 7.84) vs 6.61 (4.09, 7.84). After accounting for site, age, mechanism of injury, ISS score, AIS head, and PROPPR treatment, smoking was associated with overall lower mortality at 24 hours (OR=0.09, p<0.001) and at 30 days, with the primary difference occurring at < 6 hours (OR=0.04, p=0.002) in contrast to ≥ 6 hours (OR=0.48, p=0.037). Deaths due to exsanguination/hemorrhage or TBI were decreased in smokers (1.4% vs 15.6%, p<0.001 and 3.6% vs 10.6%, p<0.01, respectively). Admission cytokine levels of IL-6 (p=0.002) and MCP-1 (p=0.012) were significantly lower in the smoking group. Serum cotinine, a metabolite of nicotine, levels for the mortality group will be measured to confirm smoking status.

Conclusions: Smoking appears to have a protective effect in the severely injured trauma population, reducing early deaths as a result of hemorrhage or TBI in patients living to hospital arrival. This may be due to an attenuation of the early inflammatory response.
30-day Mortality in Whole Cohort

- Smokers (N=140)
- Non-smokers (N=540)

Log-rank P < 0.001
ABSTRACT

Surgical Drains and Their Influence on Patient Recovery Following Equatable Plastic Surgeries

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Sponsored by: David J. Wainwright, MD; UT Physicians Plastic and Reconstructive Surgery
Supported by: UT Physicians Department of Plastic and Reconstructive Surgery
Key Words: Surgical drains, tubing length, patient outcomes

BACKGROUND: The use of post-operative surgical drains is indicated in patients who have an accumulation of fluid or prophylactically in patients who are at a high risk for developing fluid-related complications following a surgical procedure. Drawbacks to their use include an increased risk of post-procedure infections and increased duration of hospital stays. Furthermore, early removal of surgical drains equates to better outcomes and reduced rates of infection. Complications of surgical drains include occlusion of tube, site infection, clot formation, and poor placement resulting in hernia or perforation. A review of the literature found that most existing studies evaluating surgical drain management have addressed the necessity of drain use overall, and not alterations in the drain or its care to generate improved outcomes. This prospective research study was designed to assess how a drain factor (e.g., tubing length) can affect patient outcomes post-operatively.

MATERIALS AND METHODS: Patients who were undergoing any plastic surgery operations that stipulated the use of bilateral drains were recruited into this study. A total of 14 patients over the span of three months were enrolled in this study. Upon initiation of incision closure following the completed surgery, the fenestrated end of the Jackson-Pratt drains were placed bilaterally and symmetrically in the generated open space. Side randomization was established through a blind choice by an objective observer, and one tubing was cut to a 60 cm length and the other tubing was cut to 30 cm. Before leaving the operating suite both drains were emptied and their initial volume measured. For their post-operative course, patients were given a demonstration on proper drain emptying and care, and given both a drain emptying schedule and evaluation forms covering associated factors such as pain, inflammation, infection, and convenience. Once drain volumes decreased to less than 50 cc per 24 hours the drains were removed in-clinic and an exit interview covering full drain experience was conducted.

RESULTS: Four out of fourteen patients in the current sample size experienced greater drainage volume from the 60 cm drain vs the 30 cm drain with the mean percent increase being 16.5% (2.6-39.9%). Ten out of fourteen patients had greater drainage volume from the 30 cm drain vs the 60 cm with a mean percent increase of 28.3% (16.1-36.8%). While the mean average drainage volume for the 30 cm group was larger than that of the 60 cm group, this was found to not be statistically significant (p=0.24). In addition, two patients experienced greater pain in the 30 cm drain site in comparison to the opposing 60 cm site, and four patients experienced greater clotting in the 60 cm drain site versus the 30 cm side.

CONCLUSION: While more patients enrolled in this study experienced greater drain output on average from a Jackson-Pratt drain cut to 30 cm versus their 60 cm counterparts, this margin was found to not be statistically significant. Therefore, we would fail to reject the null hypothesis.
which is that no clinical difference exists between patient outcomes when utilizing a 30 cm drain tubing in comparison to a 60 cm drain tubing. Also, there appears to be a tendency for shorter drains to have increased pain, and this is speculated to be due to being pulled on more often. Longer drains were shown to have a trend of clotting, which is likely due to the nature of increased length allowing for more area to clot. The relatively low power (0.45) of this study may have contributed to the failure to reject the null hypothesis. Further data collection and increased sample size may serve to illustrate an appreciable difference.
ABSTRACT

Pulmonary Surfactant Protein-A Induced Degradation of Toll-Like Receptor-4 Through the Ubiquitin-Proteasome Pathway

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Sponsored by: Joseph L. Alcorn, PhD, Department of Pediatrics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35DK007676-24
Key Words: Necrotizing Enterocolitis, Surfactant protein A, UPP

Background: Necrotizing enterocolitis (NEC) is a disease that affects 7% of premature newborns (weighing between 500 – 1,500 g) with a 20-30% mortality rate. NEC is characterized by severe inflammation of the gastrointestinal lining which has been shown to be largely mediated by toll-like-receptor-4 (TLR4). Surfactant protein A (SP-A) is mainly produced in the lungs where it plays an immunomodulatory role on TLR4 activity and expression. In a previous study using a mouse model of NEC, gavaged SP-A reduced both TLR4 and IL-1β in the ileum. The exact mechanism of this downregulation is not elucidated; however, it has been observed that the proteasome inhibitor MG132 ablated the ability of SP-A to decrease TLR4 expression. So I hypothesized that exposure of gastrointestinal epithelial cells to SP-A leads to degradation of TLR4 through the ubiquitin proteasome pathway (UPP).

Methods: SP-A was extracted and purified from previously collected bronchioalveolar lavage during the first few weeks. Gastrointestinal epithelial cell lines HT-29 (Human colonic cell line) and IEC-6 (Rat intestinal cell line) were incubated in the presence or absence of SP-A and in the presence or absence of various proteasome inhibitors (MG-132, bortezomib, or carfilzomib). The expression of TLR4 was detected using western immunoblot analysis. Immunoblots were treated with TLR4 and β-actin antibodies. Bands were visualized with chemiluminescence and quantified using a storm 840 phosphor imager.

Results: Adding the proteasome inhibitor bortezomib did not increase TLR4 levels in either HT-29 or IEC-6 cell lines as expected, and instead decreased TLR4 even further compared to cell lines incubated with SP-A alone. Similarly, TLR4 expression failed to increase in cell lines treated with carfilzomib and MG-132.

Conclusion: The use of proteasome inhibitors was expected to cause an increase in TLR4 expression relative to cells treated solely with SP-A; however, MG-132, bortezomib, and carfilzomib all failed to ablate the ability of SP-A to downregulate TLR4. This leads us to believe that TLR4 is not being degraded through the ubiquitin proteasome pathway as previously thought, but instead depends on lysosomal proteolysis. For this reason, future studies should concentrate on lysosomal inhibitors chloroquine, bafilomycin, and the endocytosis inhibitor dynasore to test this newfound hypothesis in our system.
ABSTRACT

Cytochrome B reductase 1 (CYBRD1) in red blood cells (RBC) of patients with hemoglobin SC (HbSC) and hemoglobin SS (HbSS) forms of sickle cell disease (SCD).

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Sponsored by: Richard J. Kulmacz, PhD, Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35DK007676-24; American Heart Association, 16GRNT29170013
Key Words: cytochrome B reductase 1, sickle cell disease, hemoglobin SC

BACKGROUND: HbSC (HbS (α2βS2) and HbC (α2βC2) compound heterozygote) individuals account for 15% of SCD patients in the US. HbSC individuals generally have milder clinical manifestations than HbSS patients, but the reasons for this difference are not completely understood. SCD pathology results from chronic cycles of ischemia / reperfusion, exacerbated by the consequently increased vascular oxidative stress. Ascorbic acid, an essential plasma antioxidant, tends to be depleted in SCD patients. CYBRD1, a RBC membrane protein, regenerates plasma ascorbic acid through an electron transfer mechanism. Recent reports have shown that HbSC RBCs experience oxidative stress that is intermediate between HbSS and HbAA RBCs. Initial immunoblot results from our lab suggested that HbSS RBCs have less CYBRD1 than HbAA RBCs (healthy controls), and CYBRD1 isoform patterns on immunoblots suggested there was less post-translational modification in CYBRD1 from HbSS RBCs. Thus, we hypothesized that RBC CYBRD1 levels and isoform patterns in HbSC patients would be intermediate between those of HbSS patients and HbAA controls.

METHODS: Blood samples were collected at UTHSCH Comprehensive Sickle Cell Center from HbSC (N=6) and HbSS (N=8) patients, and healthy African American volunteers (N = 8). Procedures for isolation of RBC membranes and quantitative immunoblot analysis of CYBRD1 content and isoform distribution have been described. (Kulmacz et al. (2015) Blood 126,2170)

RESULTS: HbSS (N=5) and HbSC (N=4) RBCs had similar CYBRD1 levels (1.13 ± 0.20 vs 1.06 ± 0.24 ng/μg membrane protein, respectively; P<0.7). No difference was seen in CYBRD1 content between HbSS and HbAA (N=5) (1.13 ± 0.20 vs 1.18 ± 0.20 ng/μg membrane protein, respectively; P<0.7) or between HbAA and HbSC samples (1.18 ± 0.20 vs 1.06 ± 0.24 ng/μg membrane protein, respectively; P<0.4). However, the CYBRD1 modification index values were significantly different: HbAA, 80 ± 7 % N=8; HbSS, 61 ± 8 % N=8 (P<0.0002 vs. HbAA); and HbSC, 73 ± 4 %, N=6 (P<0.006 vs. HbSS; P<0.06 vs. HbAA).

CONCLUSIONS: Our findings do not support the hypothesis that RBC CYBRD1 content differs between HbAA, HbSC, and HbSS RBCs. However, we believe that known differences in hematocrit between HbAA, HbSC, and HbSS individuals will still lead to differences in the total amount of circulating CYBRD1, and thus the total ascorbate recycling capacity. Our observation
of differing CYBRD1 isoform patterns between healthy controls and SCD patients raises the possibility of altered regulation of CYBRD1 function in SCD patients.
ABSTRACT
Interprofessional Education through Standardized Patient Cases

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Sponsored by:  Jennifer L. Swails, M.D., Department of Internal Medicine
Supported by:  In part, U.T. System Patient Safety Committee Medical Education Grant
Key Words:  Interprofessional Standardized Patient Simulations

According to the Joint Commission, poor communication contributed to 62% of sentinel events reported in 2012-2014. In response to this opportunity to improve patient safety, the major accrediting bodies for medical professionals require that students be prepared “to function collaboratively on health care teams.” Our project aimed to utilize interprofessional (IP) standardized patient (SP) cases to improve students’ communication and teamwork skills.

A team of IP faculty from each of the five UT Health professional schools was recruited to collaborate in designing two SP cases. A simulated electronic medical record was created for each case in Practice Fusion. Students completed assignments in Canvas, including pre- and post-tests, online teamwork skills lectures, a review of relevant medical literature, and a worksheet each team filled out during the case. The students were tasked with completing the Interprofessional Collaborative Competency Attainment Survey (ICCAS) before and after the cases. Teamwork skills were evaluated by the SPs using checklists and through verbal SP feedback to each team. Students offered feedback about the case both verbally and electronically through the Canvas website.

A pilot group of 38 students participated in the SP simulations in April 2017. An additional 92 students participated in one of the two cases in July 2017. The pretest ICCAS was completed by 99% of the assigned students and 78% of the students completed the post-test ICCAS. The average ICCAS scores were compared using a two-tailed nonpaired t-test and both cases showed significant improvement. For the in-patient case, the pretest average was 5.32 and the post-test average was 6.57 with a p-value of <0.05. For the ambulatory case, the pretest was 6.17 and the post-test was 6.73 with a p-value of <0.05. Subjective student feedback emphasized the importance of the patient and the team in providing optimal care.

These cases were implemented into the curriculum of the medical school, dental school, and nursing school, with continued participation of students from public health and bioinformatics schools on a volunteer basis.
ABSTRACT
Progressive hemorrhagic injury and traumatic brain injury inflammation in the context of polytrauma

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Sponsored by:  Charles E. Wade PhD, Center for Translational Injury Research (CeTIR)
Supported by:  CeTIR
Key Words:  Traumatic brain injury (TBI), Progressive hemorrhagic injury (PHI), inflammation

Progressive hemorrhagic injury (PHI), the early expansion of intracranial hemorrhage presumably secondary to derangements in coagulation and inflammation, is a devastating complication of traumatic brain injury (TBI). Studies exploring PHI pathophysiology in polytrauma, which itself is associated with secondary inflammatory aberrations, are limited. We predict that PHI is associated with greater clinical inflammation compared to patients with polytrauma or stable hemorrhage (SH) alone.

We retrospectively reviewed a cohort of highest-level activation trauma patients with prospectively collected data. Using radiological and clinical criteria, patients were separated into SH with polytrauma (n=7), PHI with polytrauma (n=23), or polytrauma alone (n=54). Data for standard demographic and clinical variables were collected via chart review. Inflammatory cytokine/chemokine marker profiling was conducted across 8 timepoints in the first 72 hours of admission. Data was compared for TBI vs. non-TBI patients and PHI vs. SH patients using Cox 24hr mortality model, univariate analysis, and Fisher’s exact test.

Patients with TBI demonstrate significantly greater inflammation for IL-6, IL-8, MCP-1, and G-CSF from 2-12hrs after admission compared to non-TBI. PHI was associated with higher mortality (p = 0.0309) and demonstrated significantly greater inflammation in IL-6, IL-8, MCP-1 and G-CSF (p < 0.05). Increasing levels of IL-6 was associated with a two-fold increased risk of mortality (HR 2.06, 95%CI 1.35-3.14, p = <0.001).

Patients with PHI demonstrate exaggerated inflammatory responses and have poorer clinical outcomes including mortality. These novel findings provide a molecular understanding of PHI specific inflammatory dysregulations; thus, yielding targets for improved intervention and biomarkers for improved prognostication.
ABSTRACT

Determination of Coagulation Kinetics Using a Novel Linear Thromboelastometry Device

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Sponsored by:  Charles S. Cox, JR. MD, Department of Pediatric Surgery, Brijesh Gill MD, Department of Surgery

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

Key Words:  TEG, Thromboelastography, Thromboelastometry, Trauma, Novel Device

Introduction: Thromboelastography (TEG) demonstrates clinical utility in multiple surgical fields including general, trauma, hepatic, and cardiac surgery. We describe a novel linear thromboelastometry device (LTD) driven by a microelectromechanical system (MEMS) with the potential for scaling to portability. The LTD demonstrates similar coefficients of variation as TEG in normal human control subjects. We hypothesize that this device will correlate with TEG values in trauma patients.

Methods: Venous blood was collected from healthy adult volunteers and Level 1 trauma patients into citrate tubes. Recalcified blood is injected into a well mounted on a MEMS driven translational stage. As the blood clots, and a platelet/fibrin mesh forms, an increasing force acts on the unfixed end of a paddle probe inserted in the sample. This force is measured optically as deflection of the probe. Clot formation metrics were defined as follows: maximum amplitude of probe deflection (MA), time to first evidence of probe deflection (R), and time to reach an established deflection (K). Blood from a single individual was tested in triplicate for 3 consecutive days to determine single person variability of the device. To test population variability of the device, blood from four individuals was tested in duplicate. To test the sensitivity of the device, blood samples were diluted with phosphate buffered saline (PBS). 11 Level 1 trauma patients were tested in the LTD and TEG to demonstrate their correlation.

Results: Coefficient of variation (CV) is smaller in the LTD than TEG for R (CV=0.232, CV=0.294) and K (CV=0.230, CV=0.435) in single person variability and MA (CV=0.045, CV=0.095) in population variability. Hemodilution with PBS demonstrated a strong correlation between platelet count and MA in the new device (R² = 0.978), and LTD MA correlated strongly with TEG MA (R² = 0.934). The new device detected a signal in as little as 5% blood by volume, while TEG detected a signal at 15% blood by volume. There was a strong correlation between TEG MA and LTD MA in the trauma patient population (Pearson r=0.6854, P<0.05).

Conclusion: This preliminary study demonstrates repeatability and clinical relevance of the LTD. The LTD shows a strong correlation with TEG values in trauma.
ABSTRACT
Lymphatic Contribution to Peripheral Arterial Disease and Chronic Venous Disease

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Sponsored by: Eva Sevick-Muraca Ph.D., John Rasmussen Ph.D., Center for Molecular Imaging
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2T35DK007676-22
Keywords: Lymphatics, Peripheral Artery Disease, Chronic Venous Disease, Peripheral Vascular Disease

Peripheral Arterial Disease (PAD) and Chronic Venous Disease (CVD), are leading causes of disability in people older than 50 years of age. Evidence suggests that the lymphatics contribute to the etiology of PAD and CVD. In PAD, functioning peri-adventitial lymphatics are essential for reverse cholesterol transport in arterial walls, preventing plaque accumulation. Likewise in CVD, reduced numbers of lymphatic vessels and increased lipids have been found in the adventitia of incompetent veins with varicosities. If lymphatic dysfunctions are found to contribute to PAD and CVD, then therapeutic strategies to modulate the immune-lymphatic system could be used to help manage PAD and CVD. This project evaluates lymphatic anatomy and function of 40 patients with early CVD (CEAP 0-4) and/or mild to moderate PAD (Rutherford 2-5 disease) using near-infrared fluorescence lymphatic imaging (NIRFLI). To do so, indocyanine green (ICG) was administered intradermally in the lower extremities after which, NIRFLI is performed by illuminating the skin with diffuse laser diode light and collecting filtered fluorescent light emanating from the ICG-laden lymph. Using NIRFLI images, lymphatic anatomy and function were analyzed in early CVD and PAD patients. In each of three subjects imaged to date, evidence of lymphatic dysfunctions including dermal backflow, and dilated, tortuous, and/or segmented lymphatic vessels, and impaired lymphatic pumping was found. The PAD subject with Rutherford stage 3 disease presented with non-linear vessels, dermal backflow, and lymphatic reflux in both legs. The first of two CVD subjects presented with C3 disease on the right leg and C5 disease on the left leg. The right (C3) leg presented with segmented and dilated vessels. In the left groin there was dermal backflow, suggesting lymphatic congestion. However the etiology of congestion is unknown and it cannot be concluded that this congestion contributes to or is a result of the CVD. Lymphatic pumping was present bilaterally, but was infrequent. The second CVD subject presented with bilateral C4 disease. The lymphatics in the left and right legs were segmented and dilated, though vessels were better defined in the left leg as the right leg exhibited possible dermal backflow. Pumping events were frequent, but with 50% more pumping events in the left leg. The segmented vessels in the subjects may be a result of lymphatic varicosity or unequal accumulation of ICG within individual lymphangions. The reflux found in the PAD subject suggests lymphatic valve dysfunction. Reflux was observed in a prior patient with an arterial component to their disease. Whether lymphatic reflux is a hallmark of PAD may be better determined as more PAD subjects are enrolled. Using NIRFLI, lymphatic dysfunction has been observed, as compared to previously imaged healthy subjects. As this study
continues, evidence is growing that lymphatic dysfunction is involved in the etiology and/or progression of PVD and CVD.
ABSTRACT

Biomechanical Study Analyzing the Maintenance of Interfragmentary Compression with a Position Screw

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Sponsored by: James F. Kellam, MD; Catherine Ambrose, PhD; Department of Orthopedics, McGovern Medical School

Supported by: James F. Kellam, MD; Catherine Ambrose, PhD; Department of Orthopedics, McGovern Medical School; McGovern Medical School- Office of The Dean

Key Words: Position, screw, maintenance, interfragmentary, compression

Introduction: Interfragmentary fracture site compression enhances fracture union by increasing the fracture site contact area, enhancing fracture stability and decreasing the stress on the orthopedic implant. Lag screw fixation is the gold standard in achieving interfragmentary compression. However, in certain circumstances it may be an ill-advised technique such as in osteoporotic bone, possibly leading to iatrogenic fracture and fixation failure. In these cases, a position screw is recommended. A position screw holds the fracture fragments in the reduced position only. Utilizing this technique can make operating in certain circumstances where lag screw placement is difficult much easier, saving time, money and potential complications.

Objectives: The aims the study are to prove that: 1) the compressive force generated by a reduction clamp can be maintained by the position screw and 2) a conventional lag screw will maintain the reduction clamp generated compression force and not dissipate on clamp removal.

Methods: Twelve 4th generation composite bone models had identical 45-degree oblique fractures created. Commercially available self-tapping bone screws (thread diameter of 4.5mm and a core diameter of 3.2 mm) were used. One group of 6 models was designated as the “lag screw” group (LS) and one was designated as the “position screw” group (PS). For the LS, a glide hole of equal diameter to the screw thread diameter was drilled perpendicular to the fracture site in the near cortex and then the thread hole (diameter equal to screw core diameter) was drilled in the far cortex. For the maintenance screw group, the same technique is employed but no near cortex glide hole is drilled, thus creating no compression. For each bone, the simulated fracture was reduced and stabilized with a reduction clamp tightened to the maximal compression force manually. Two Tekscan pressure sensors (in N) at 180 degrees to each other were placed between the two fracture fragments to measure the compression as the clamp and respective screws were applied and the results were averaged. The clamp was then removed and another measurement was recorded.

Results: For the PS group, clamp compression yielded an average force of 169.9 N across six trials (N=12 to account for two sensors per trial). Screw and clamp compression yielded an average force of 122.3 N. Screw only compression yielded an average force of 42.4 N. ANOVA and Tukey post-hoc test found that the mean forces of screw group was significantly different from the other two groups but there was no significant difference between the clamp/screw and clamp. For the LS group, (N=11 because one sensor did not read measurements so its values were eliminated) clamp compression yielded an average of 93.4 N. Clamp and screw compression yielded an average of 272.1 N. Screw
only compression yielded an average force of 259.6 N. The ANOVA and Tukey post-hoc test found that the mean forces of the screw only and clamp/screw group were not significantly different from each other. However, there was a significant difference between the clamp only group and the others. A graphical depiction of these results can be found in Figure 1.

Conclusion: While the lag screw will maintain and greatly increase the compression force generated by the reduction forceps, a position screw cannot maintain the compressive force generated by the clamp. In fact, as demonstrated by our data, the compressive forces with the position screw significantly decreased when it was inserted with the clamp in place and decreased even more when only the screw was present. We surmise that this is because the threads of the position screw are on both sides of the fracture site, distracting the fracture site and reducing interfragmentary compression. In summary, the position screw is not an adequate replacement for the lag screw to hold the compressive force generated by a reduction clamp. Further studies should be conducted in cadaveric bone to see if this conclusion holds true.

Appendix:

Figure 1. Mean compressive forces generated for each type of compression across six trials using a maintenance screw.

Figure 2. Mean compressive forces generated for each type of compression across six trials using a lag screw.

Note: SE= Standard Error.
★ denotes significant difference between two groups (p <.05).
ABSTRACT

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Sponsored by: Leorah Freeman, MD, PhD, Department of Neurology
Supported by: FCMSC Grant/Scholarship Award + UTHealth Department of Neurology
Key Words: Enhanced Regional Cerebral Perfusion Following Acetazolamide: Preliminary Results

Enhanced Regional Cerebral Perfusion Following Acetazolamide: Preliminary Results

Background: Clinical symptoms in multiple sclerosis (MS) typically occur as a result of focal inflammation associated with demyelination and axonal damage within white matter lesions. Symptoms can be transient for many patients during the initial stage of the disease with some varying degrees of clinical improvement, dependent upon whether inflammation subsides and tissue undergoes repair. Observational studies have shown that these alterations in tissue perfusion were evident prior to regional atrophy, suggesting that a primary abnormality in the cerebral vasculature might contribute to cerebral hypoperfusion, and evolution of MS pathology. If reduced cerebral perfusion is important in disease progression, then improving blood flow might lessen, or even reverse this process, thus favoring repair. While transient increases in CBF are noteworthy and documented, sustained change in CBF might be necessary to impact lesion evolution and potentially limit or partially reverse clinical disability.

Hypothesis: Acetazolamide (ACZ) has a good safety and tolerability profile, and is known to enhance cerebral perfusion. Our central hypothesis is that ACZ may provide long-lasting global increases in CBF and thus have sustained beneficial effect on focal lesion outcome.

Significance: There are currently several potent disease modifying therapies (DMTs) available to treat patients with MS which have all been shown to decrease the potential for new injury. Despite their anti-inflammatory properties, DMTs are not known to alter cerebral perfusion and no therapy has thus far been rigorously evaluated to show whether improved blood flow affects lesion evolution in MS patients.

Methods: The perfuseMS study (NCT02466074) is a placebo-controlled trial to evaluate the effect of long-term ACZ therapy on lesion evolution in MS patients. Stage 1 is designed to determine the magnitude of change in cerebral perfusion after a single intravenous (IV) infusion of ACZ.

Eligible patients have stable MS either treatment naïve or on platform therapies. Absolute cerebral blood flow (CBF) was measured using pseudo-continuous arterial spin labeling (pCASL). Five MS patients received pCASL at baseline and 15, 30, 60, 90, 120, 150 and 180 min after a single IV bolus of 1 gm ACZ. pCASL was performed with a single shot gradient echo EPI sequence (TR/TE of 4300 ms/16 ms, voxel size 3 × 3 × 5 mm, number of dynamics 70, label duration 1900 ms, post label delay 2000 ms). Data were analyzed with FMRI B Software Library and FreeSurfer v5.3.0. After partial volume correction, CBF maps were registered to 3D-MPRAGE images using boundary-based registration. Brain regions were
segmented using semi-automated methods into cortex, normal-appearing white matter (NAWM), deep gray matter (DGM) and T2-hyperintense lesions.

Results: Consistent with prior reports in healthy subjects, our patients had 30%-62% increase in global CBF 15 min after ACZ. Unlike prior reports, global increases in CBF were present for up to 180 min. Increases in CBF were seen in all brain regions. CBF in cortex increased 26%-54%, NAWM by 25%-53% and DGM by 31%-74% at 15 min. While greater variability was seen in absolute CBF within lesions, the largest increases were found with 14%-105% occurred at 15 min. Similar to global kinetics, increases in CBF within brain regions were present for up to 180 min.

Conclusions: We report for the first time the kinetics of cerebral perfusion in MS patients following 1 gm IV ACZ challenge. Though greatest change in cerebral perfusion might be expected in the cortex, we found substantial increases in CBF in various brain regions including cortex, NAWM and DGM. We also found robust increases in CBF within MS lesions; areas considered injured. These results show that blood flow can be increased to lesioned tissue and supports further investigation of our hypothesis that cerebral hypoperfusion is important to lesion evolution and improving cerebral perfusion might impact tissue repair.
ABSTRACT

Put a Ring on it: Better Pediatric Pre-Induction Checklist Adherence Observed with Parent Engagement

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Sponsored by: Dr. Kuojen Tsao, MD, Pediatric Surgery
Supported by: Dr. Kuojen Tsao, MD
Key Words: Checklist adherence, parent engagement

Introduction: Patient and parent engagement in healthcare has been shown to improve compliance and outcomes in many medical disciplines, but no literature exists regarding parent engagement in the perioperative process. The World Health Organization surgical safety checklist (SSC) recommends including the parents of pediatric patients in checklist completion. At our children’s hospital, the pre-induction SSC is conducted in pre-operative holding with anesthesia, nursing and often with parents. We hypothesized that better checklist compliance would be observed when parents were engaged in checklist performance.

Methods: An observational study of pre-induction checklist adherence during non-emergent pediatric operations was performed from 2016 to 2017 during two separate 8-week periods. Adherence was defined as verbalization of each checkpoint with or without parent confirmation. Six of 13 checkpoints (patient identification, procedure, surgical site marked, weight, allergies and NPO status) containing information relevant to parental knowledge were evaluated for staff confirmation with parents. Trained observers assessed parent engagement based on: parents off their phones, not distracted, positive body language, eye contact and demonstrating an understanding of the checkpoint. Chi-square test and linear regression were used for analysis. P-value <0.05 was significant.

Results: Over the study period, 459 pre-induction checklists were observed with at least partial completion in 93.3% of cases with kappa >0.7. The mean proportion of checkpoints completed was 64.6% ± 31.1% and the proportion of fully completed pre-operative checklists was only 18.3%. Parents were present in 82% of cases and at least 1 checkpoint was confirmed with parents in 79% of checklists. Pre-induction checklist adherence was better when parents were present compared to when absent (p<0.001 for all checkpoints). Linear regression demonstrated a 1.2 (95%CI 1.0-1.3) increase in pre-induction adherence for every unit increase in parent engagement (Figure). Furthermore, meaningful completion of checkpoints by staff confirmation with parents differed significantly based on parent engagement with 93.9-100% of staff confirmation of checkpoints occurring with engaged parents compared to 0.3-6.1% in parents deemed not engaged (p<0.001).

Conclusion: Pre-induction SSC performance remains a challenge, as less than one-fifth of checklists were completed in full. However, dramatic improvement in compliance and staff confirmation of checkpoints was observed when parents were present for and engaged in the checklist process. Creating a process and training operative teams how to engage parents may increase checklist compliance and improve patient safety.
ABSTRACT

Use of autologous blood clot for human muscle derived stem cells preservation and growth

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Sponsored by: Xueqin Gao MD, PhD, Johnny Huard PhD, Department of Orthopaedic Surgery

Supported by: Start-up funding from Dr. Johnny Huard lab.

Key Words: Human muscle derived stem cells, blood clot, proliferation, apoptosis

Introduction: Previous study has shown the efficacy of fibrin clot in preserving the viability of human muscle derived stem cells (hMDSCs) when cultured in proliferation medium. The purpose of this study was to investigate if the fibrin clot itself can maintain hMDSCs survival without the use of proliferation media by culturing clot load with cells in PBS.

Methods: Six patients were recruited for the study and hMDSCs-Lenti-GFP(6X10⁵) cells were mixed with 30ml whole blood drawn from clinical patients following the IRB protocol. The formed clot was squeezed to remove residual serum. Each clot was cut into 12 pieces and placed into two wells of 6-well plate. 5 mL of proliferation medium (PM) or PBS was added to the wells respectively. One piece of the clot was taken out at various time points (0h, 1d, 2d, 3d, 4d, and 7d) and embedded in NEG freezing medium followed by snap freezing via liquid nitrogen. Cryosections were cut. GFP immunofluorescent staining was used to detect hMDSCs in the blood clot. Cell proliferation in the blood clot was detected via Ki67/GFP double immunofluorescent staining. Fluorescent images were collected using Nikon-Ni upright microscope and quantified via Image J. Student t test was performed for comparison between the two groups. Average number of cells per time point in each group was normalized to a 200X magnification field.

Results: Our results showed that GFP positive hMDSCs can be found in the fibrin clot both cultured under PM or PBS for 7 days. Quantification of GFP hMDSCs positive cells demonstrated that there is no difference between clots cultured in PM and PBS at 0h and 1d. However, there are fewer GFP positive cells in PBS cultured clots at 2, 3, and 7 day time points compared to clot cultured in PM (P=0.0043, 0.0025, and 0.021 respectively for 2, 3, and 7 day time points). Ki67/GFP double positive cells showed no significant difference between PM and PBS group at any times points.

Discussion: Our results showed fibrin clot can preserve cell survival for a short time (1d) when they are cultured in PBS without any nutrients. The total number of cells decreased overtime when the clot was cultured in PBS as compared to that cultured in PM. Although blood clot cultured in PBS did not survive as long as that in PM, cell proliferation (Ki67/GFP double positive cells) has no difference. These results are meaningful, especially in a clinical setting. If the clot can keep cells alive in the first 24 hours, cells in the clot can get nutrients from the blood circulation and then be able to differentiate and repair tissues, such as meniscal tissue. Staining for caspase 3 was also performed to determine if there is difference in cellular apoptosis between the PM and PBS group and is currently under analysis. We conclude that blood clots can be used as an autologous scaffold for hMDSCs mediated tissue repair.
ABSTRACT

Comparative Analysis of subdural grids vs. stereo-electroencephalography in the evaluation of intractable epilepsy

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Sponsored by: Nitin Tandon, MD, Department of Neurosurgery
Supported by: Nitin Tandon, MD, Department of Neurosurgery; McGovern Medical School – Office of Educational Programs

Key Words: Electrocorticography, Intractable Epilepsy, Epilepsy surgery, Complications, Efficacy

INTRODUCTION: Subdural Electrodes (SDE) have been the mainstay for the evaluation of patients with non-lesional or ill-defined focal epilepsy in North America. The advent of stereo-electroencephalography (SEEG) over the past decade has transformed the process of the localization of regions responsible for seizure onsets, for resection/ablation/neuromodulation, in a minimally invasive fashion. Both SDE and SEEG techniques have relative advantages, but in many patients, either one could be applied. We sought to compare the relative efficacy, morbidity and seizure outcomes following these two approaches.

METHODS: All 260 intracranial procedures, consecutively performed by a single neurosurgeon from 2004 to 2017, were identified using a prospectively compiled surgical database. Patient demographics, characteristics of epilepsy, duration of monitoring, procedural morbidity and eventual outcomes were determined. We computed the opiate requirements following each of these intracranial evaluations as a surrogate for the pain associated with each approach. Comparisons between groups were made using unpaired t-tests and chi-squared tests to evaluate distinctions.

RESULTS: Both SEEG (n=121) and SDE (n=139) groups were similar in age (30.1 ± 12.2 vs. 30.6 ± 13.8 years), gender (SEEG = 47.1% male; SDE = 43.9% male) and duration of epilepsy (16.4 ± 12.0 years vs. 17.2 ± 12.1 years). A much larger proportion of SDE patients (13.7%) received blood products during surgery compared with SEEG patients (0.8%) (p = 0.0001). Pain medication requirements were also much greater in the SDE vs the SEEG group (355.8 ± 232.9 mg vs 201.4 ± 175.5 mg). The duration of intracranial monitoring in these two groups was comparable (SEEG = 7.7 ± 3.9 days vs. SDE = 8.1 ± 2.8 days). Similar numbers of SDE (6) and SEEG (7) patients underwent placement of additional electrodes after the initial implant, during the same hospital stay, to further delineate the seizure onset site. There were 7 symptomatic hemorrhagic sequelae and two infections in the SDE cohort with no clinical complications in the SEEG cohort (p = 0.004). Only one patient from the SDE cohort experienced long-term neurological sequelae related to the intracranial evaluation. A greater proportion of SDE patients underwent resective or ablative surgery (91.4%), compared with SEEG patients (72.7%, p < 0.0001). None of the SDE patients and 4.1% of SEEG patients underwent placement of the RNS device. 8.6% of SDE patients and 14.1% of SEEG patients were not thought to be candidates for further cranial intervention. The seizure
outcomes (Engel I or II) in this group, at 6 months post-resection, trended in favor of SEEG (83.1%) relative to SDE (65.5%, p = 0.01).

**DISCUSSION:** SEEG and SDE have significantly distinct procedural morbidities: 6.5% (SDE) and 0% (SEEG), p < 0.05, associated with distinct pain medication requirements, which should factor into decision making when patients with pharmaco-resistant epilepsy are being considered for an intracranial evaluation. However, long term deficit rates related to either type of electrode placement are small. A smaller proportion of patients undergoing SEEG evaluations undergo resective or ablative surgery, likely related to the fact that some patients in this cohort may be distinct, less well localized epilepsy population compared to those undergoing SDE placement. There was a noticeable trend towards a better outcome in the SEEG cohort at 6 months post-resection (p =0.01).
ABSTRACT

Role of Circulating Tumor Cells as a Biomarker of Disease Progression in Prostate Cancer Patients

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Class of 2020

Sponsored by: Robert J. Amato, DO, Division of Oncology
Supported by: Robert J. Amato, DO, Division of Oncology; The University of Texas at Houston Medical School—Office of The Dean
Key Words: Circulating Tumor Cells, Prostate, Cancer, Biomarkers

Introduction: Prostate Cancer is the most common cancer among men and the third leading cause of cancer death in men. While prostate specific antigen (PSA) remains an integral part of the clinical management of prostate cancer, there lies a need for a more sensitive and specific method of monitoring treatment response and cancer progression. Circulating tumor cells have gained significant interest in recent years and have potential to serve as a valuable biomarker for prostate cancer.

Methods: Blood samples were collected for 17 patients over multiple time points and processed using the AxonDx nCyte™ System. This system relies on a proprietary cancer cell detection cocktail in conjunction with an epi fluorescence scanning microscope for the enumeration of CTCs. Individual patient’s CTC counts were compared with longitudinal PSA measurements and radiographic findings.

Results: CTCs were enumerated from all 17 patients. CTC values were found to vary largely between patients and longitudinally in the same patient. CTC values ranged from 0-6.2 cells/ml. Of the 3 patients with greater than 4 CTCs/ml, 2 patients had evidence of active disease, either local viable tumor or bony metastases. One of these patients progressed and died of their disease. Of the 14 patients with CTC values that never went above 4 CTCs/ml, 2 patients had evidence of progressive metastatic disease and elevated PSA levels. For the remaining patients who did not have PSA or radiologic evidence of disease progression, CTC values obtained varied longitudinally, ranging from 0-3.5 CTCs/ml. In most cases, there appears to be little clinical significance in these fluctuations. For a few of these patients there was an isolated elevation in CTC value with a simultaneous falling PSA.

Discussion: This study demonstrates that there is a correlation between CTC values and the current disease state. Based on these findings CTCs show promise as an additional way of monitoring disease progression in prostate cancer patients. Future studies with a larger patient cohort should be conducted to establish the utility of CTCs as a biomarker of disease in prostate cancer patients.
ABSTRACT

Optimizing the Dosing of Chemotherapy Pharmacokinetics in Obese Cancer Patients

TAMMY HOAI TRINH  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Judith A. Smith, B.S., PharmD, Department of Obstetrics and Gynecology
Supported by:  HOPA Research Foundation
Key Words:  Dosing, Chemotherapy, Obesity, Actual BSA, Assigned BSA, Capped BSA

Introduction: Obesity is associated with worse cancer outcomes. While determinants of response are multifactorial, poorer prognosis might be due to inadequate dosing through the common practice of using an assigned body surface area (BSA) to calculate chemotherapy doses in obese patients. In general, obesity is known to alter the volume of distribution and clearance of medications; however, there is limited pharmacokinetic data for most chemotherapy agents in the setting of obesity. Furthermore, many agents exhibit non-linear pharmacokinetic behavior, making it difficult to define and determine the impact of changes in dose on systemic exposure. The aim of this study is to understand the pharmacokinetic differences of the nonlinear agents, paclitaxel and cisplatin, in obese patients when dosed on actual versus assigned BSA or capped BSA. This data will be used to provide additional guidance for appropriate dose adjustments in clinical practice.

Methods: A total of sixty patients will be recruited to this study from the UTHealth-Memorial Hermann Cancer Center in the Texas Medical Center (TMC). Ten obese/overweight patients and ten control (non-obese) patients will be enrolled per study arm for each of the regimens being evaluated: paclitaxel + carboplatin once every three weeks (N=20), paclitaxel weekly + carboplatin (N=20), or cisplatin/XRT (N=20). For the first cycle, patients in the treatment group will be randomized into two groups with paclitaxel or cisplatin dose calculated based on either actual BSA or the respective assigned/capped BSA. They will receive the alternate BSA in the second cycle. For cycle 3 and beyond dosing is based on primary oncologist’s discretion. On the day of infusion for cycles 1 and 2, blood samples are collected for analysis via validated assays using either PaperSpray mass spectrometry or HPLC-UV for paclitaxel or atomic absorption for cisplatin. Toxicity is monitored using the MDASI QOL assessment tool for cycle 1 and 2 and chart notes are monitored through cycle 6.

Results: This study is still ongoing with anticipated enrollment to conclude in December 2018. To date 8 patients (3 obese, 5 control) have been enrolled on the paclitaxel + carboplatin once every three weeks study arm. More toxicity has been observed in this study arm. Three patients (1 obese, 2 control) have been enrolled on the paclitaxel weekly + carboplatin study arm. More toxicity has been observed in this study arm. Two patients (2 obese) have been enrolled on the cisplatin/radiation study arm. Collection of toxicity data for the cisplatin/radiation study arm is
ongoing. Analysis of differences in plasma concentrations for all patients is ongoing and will be presented on poster.

**Conclusion:** Preliminary results show that obese cancer patients who received full-weight based doses of paclitaxel and cisplatin have higher levels of toxicity compared to their normal weight counterparts. These results support using assigned BSA for the calculation of chemotherapy dosing in obese patients.
ABSTRACT

Prognostic Value of Ambulatory Blood Pressure Associated with Left Ventricular Hypertrophy in Children Evaluated for Primary Hypertension

GRACE TRUONG

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Class of 2020

Sponsored by: Joshua Samuels, MD., MPH., Department of Pediatrics
Supported by: Joshua Samuels, MD., MPH., Department of Pediatrics
Key Words: ABPM, BMI, Pediatrics, Ambulatory

Hypertension is a prominent problem in both adult and pediatric populations. Ambulatory blood pressure monitoring (ABPM) is a 24-hour study that is the testing method of choice for analysis of pediatric blood pressure. The primary goal of this retrospective chart review is to identify correlations between ABPM summary statistics, including demographics, average BP, BMI and current medication regiment, and measures of heart function seen on echocardiography (Echo), specifically the presence of left ventricular hypertrophy (LVH). Chart review was done on all patients born after 1995 who underwent ABPM testing as patients of UTHealth Pediatric Hypertension Clinic from January 1st, 2015-December 31st, 2016. Data analysis suggests that BMI is the only significant independent predictor of LVH, with other established factors like gender and clinical BP values showing insignificant correlation. This conclusion suggests that a change should be made in the primary criteria for cardiac work-up to place a stronger focus upon BMI.
ABSTRACT

Using Image Analysis Software to Assess Morphological Changes in Cutaneous Neurofibromas over the Course of Treatment with an mTOR Inhibitor

CONNOR VERSHEL

Sponsored by: Keri Smith, PhD, Department of Pathology
Key Words: Neurofibromatosis, image analysis, pathology

Neurofibromatosis is a genetically inherited disorder resulting from defects in the Neurofibromin 1 (NF1) gene. Most adults with neurofibromatosis type 1 develop benign tumors that are composed of Schwann cells, fibroblasts, mast cells, and vascular components, and that manifest as cutaneous, spinal, or plexiform lesions.

Neurofibromin normally suppresses the oncoprotein Ras. When Ras protein remains unsuppressed, it activates the mTOR pathway which decreases apoptotic activity, causing cellular proliferation. Thus, we performed an interventional study to determine if treatment with oral mTOR inhibitor would reduce the size of cutaneous lesions in patients with neurofibromatosis. We hypothesized that mTOR inhibitor treatment would induce tissue remodeling in the cutaneous neurofibromas, causing changes in cell type and collagen composition in the lesions.

We obtained 4 mm punch biopsies of lesions were from subjects at initiation of treatment, 3 months, and 6 months, and the tissue was fixed in formalin, embedded in paraffin, and sectioned for H&E staining. Slides were digitized using a Motic Easy Scan Pro system, and 5 representative images at 20X magnification were saved for each biopsy. We identified 4 main cell types in the tissue sections based on shape and staining properties: round cells, comma cells, spindle cells, and mast cells. We selected 50-100 examples of each cell type to use as training sets for the learning algorithm built into inForm 2.1 image analysis software. All biopsy images were then analyzed to quantify cell types and collagen density.

The results of our image analysis revealed significant heterogeneity among lesions, with obvious changes over the course of treatment. Overall, there was a significant increase (p = 0.009) in collagen density after 6 months of treatment, and the density of collagen negatively correlated with the percentage of round cells in the tissue (p=0.007). Overall changes in cellular composition were not significant over time, with the exception of an increase in percentage of comma-shaped cells from 3-6 months of treatment. Although much is still unknown about the cellular components of neurofibromas, our results suggest that some level of tissue remodeling could be occurring within the lesions in response to treatment. Future studies should aim to determine specific activation pathways that are affected and how to efficiently target them.
ABSTRACT

Effects of Antihypertensive Medications on the Success of Kidney Transplantation

ALAN VU  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Donald A. Molony, MD, Department of Internal Medicine; Joshua A. Samuels, MD, MPH, Department of Pediatrics

Supported by:  NIDDK/NIH T35; Cynthia Bell, Department of Pediatrics

Key Words:  Antihypertensive, Kidney Transplantation, Allograft Failure

Introduction:  Hypertension complicates the outcomes of kidney transplantation, leading to cardiovascular complications and decreased kidney graft survival.  There are epidemiologic data to support a hypothesis that cardiovascular inflammatory state related to the type of antihypertensive therapy choice pre-transplant might impact allograft survival post-transplant.  In this study, we explore the effects of antihypertensive use prior to kidney transplantation on graft survival and mortality.  The major types of antihypertensives interrogated in this study are calcium channel blockers, thiazide diuretics, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), and beta blockers.

Hypothesis:  We hypothesize that there will be significant differences in allograft outcomes of hypertensive patients based on their antihypertensive treatment prior to transplantation while on dialysis.  There is evidence of improved vascular outcomes in hypertensive patients on ACEIs or ARBs which could translate into improved outcomes in transplant patients.  Additionally, variation in antihypertensive use could potentially be an underlying contributor to discrepancies observed between genders, ethnicities, and/or diabetic status.

Method:  We began the research on antihypertensive use on graft survival using the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research Files from September 1987 to December 2013 with the permission from UNOS.  Using STATA 14.1, we analyzed differences between kidney graft survival time between patients on anti-hypertensives and those who are not, excluding patients who were retransplanted, had simultaneous pancreas transplant, or who had no known antihypertensive status.  Analyses were performed using the Kaplan-Meyer log rank test with three possible failure outcomes: (1) allograft failure (excluding graft survival after death), (2) allograft failure or death, or (3) death.  We stratified the data for ethnicity, gender, and diabetic status.  A p-value <0.05 was defined as statistically significant.

Results:  One significant limitation we had during the first phase of our study was the limited antihypertensive medication data in the UNOS database.  Thus, we require the USRDS database to access blood pressure management prescriptions.  We are currently working on analysis for the USRDS dataset and do not have the final results available.  With these results, we hope to understand whether any differences exist between specific classes of antihypertensive treatment pre-transplantation and outcomes.  These results might lead to improvements in the treatment of hypertension in the ESRD population. Clarification in which antihypertensive regimen provides...
superior outcomes will not only improve patients’ lives but also decrease the burden of allograft failure has on the health care system.
ABSTRACT

Hurry Up and Wait: Pre-Incision Delays in the Pediatric Operating Room Associated with Lower Adherence to Pre-incision Surgical Safety Checklist

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Sponsored by: KuoJen Tsao, MD, Department of Pediatric Surgery
Supported by: KuoJen Tsao, MD, Department of Pediatric Surgery; The University of Texas at Houston Medical School—Office of The Dean

Key Words: Surgical safety checklist, quality of care, perioperative care

Introduction: Operating room (OR) delays impact patient flow and resource utilization. Surgical cases are commonly tracked for delays in the patient reaching the OR. Time spent in the OR before incision is not often evaluated. We hypothesized that low adherence to the pre-induction surgical safety checklist (SSC) may be associated with pre-OR delays or longer pre-incision times.

Methods: An observational study of a convenience sample of scheduled, elective pediatric surgical cases in a tertiary care children’s hospital was performed over two 12-week periods by trained observers. Specialties included general and thoracic, urology, neurosurgery, ophthalmology, orthopedics, otolaryngology (ENT), and plastic and reconstructive surgery. Performance of the pre-induction checklist in the pre-operative area between nursing staff, anesthesia staff and patient/parents, the first phase of the SSC, was monitored. Degree of adherence to the pre-induction SSC is the proportion of checklist items completed. Pre-OR delays are institutionally defined as cases in which the patient enters the room more than 5 minutes after scheduled start. Pre-incision time was calculated as the difference between scheduled case start or room entry, whichever occurred first, and incision time. Descriptive statistics, chi², t-tests and linear regression were performed. Inter-rater reliability was determined before the start of study using Cohen’s kappa.

Results: Interrater reliability was greater than 0.70 for both years. Of the 451 observed cases, 34% had a pre-OR delay. Median total pre-incision time was 37 minutes (IQR 22-52). Mean pre-induction adherence was 84.6±21.7% and did not vary by specialty (p=0.12). Pre-induction adherence to the checklist (p=0.65) and specialty (p=0.11) were not associated with Pre-OR delays. First cases of the day were more likely to be on time (p<0.01). Longer total pre-incision times were associated with specialty (p=0.02) and worse checklist adherence (p<0.01, figure). After adjustment for specialty, case type and adherence, first cases (p<0.01), ENT specialty (p=0.03), and higher pre-induction adherence (p=0.03) remained associated with shorter pre-incision times.

Conclusions: While pre-OR delays are tracked and audited, delays in the OR before the start of surgery are not usually captured. Trying to achieve one metric of timeliness and efficiency may push the necessary preparations to the OR, ostensibly a more expensive locale. Pre-operative readiness may be reflected by pre-induction checklist performance and better measured by total pre-operative time.
ABSTRACT
CT scan guided sizing in TAVI pre-procedural planning and post procedural outcomes

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Sponsored by: Angelo Nascimbene, MD, Internal Medicine - Cardiology
Supported by: Deans Office Stipend - 2017 MS-1 Summer Research Program (SRP), Center for Advanced Heart Failure – Memorial Hermann
Key Words: Heart valve prosthesis implantation/instrumentation/methods; aortic valve insufficiency/diagnostic imaging; risk factors; transcatheter aortic valve replacement/methods; treatment outcome

Objective: The objective of this study is to identify anatomical factors, variations in implant technique that ensure successful implantation, and possible anatomical-procedural variations that have led to intraoperative complications.

Methods: We have retrospectively analyzed CT scan obtained from 261 consecutive patients who underwent TAVI with the S3-THV in our institution in 2016. TAVI patients were divided into groups based on annular anatomy and device size (20, 23, 26, 29 mm). CT annular area was calculated and utilized to determine size of the S3 valve to be implanted. Each implant was then subsequently matched with the degree of (if any) degree of aortic regurgitation (AI) after initial implant, the need of post dilatation due to residual AI after implant and the end of the procedure. Degree of post implant aortic regurgitation was determined by echocardiography at the time of procedure. Based on annular area specific volumes were determined to be loaded the initial delivery system.

Results: Out of 261 patients 37 were implanted with the 20-mm valve, 88 with the 23-mm valve, 101 with the 26-mm valve, and 35 with the 29-mm valve. Volumes at initial deployment were nominal (i.e. based on manufacturer recommendation) in 96% of cases and preemptively adjusted in 4% of cases based on operator experience guided by CT & preoperative TEE. The 9 valves requiring preemptive adjustment in the deployment system ranged from -3 cc to +2 cc. Of this subset of patients (9/261), 66% (6/9) of valves showed mild insufficiency at initial deployment that was treated with post dilatation incremental volume (0.5 to 1.5 mL). For noted insufficiencies, the valve sizing distribution is as follows: one 20 mm, two 23 mm, two 26 mm, and one 29 mm valve. After post-dilatation, 100% of valves showed reduced AI with either trace or no leak.

Of the 247 valves deployed at nominal volumes, 85% (211/247) showed no signs of aortic insufficiency (central regurgitation nor paravalvular leak) at the time of deployment. The remaining 15% (36/247) showed the following insufficiencies: 31 mild, 4 mild-moderate, and 1 significant. 23% (8/35) of 20 mm, 15% (12/82) of 23 mm, 11% (11/97) of 26 mm, and 15% (5/33) of 29 mm valves showed insufficiency after deployment. 11% (29/247) of valves, all of which showed insufficiency, were post-dilated with variable incremental volumes in the deployment system; 14% (5/35) of 20 mm valves required post-dilatation; 12% (10/82) of 23 mm valves...
required post-dilatation; 10% (10/97) of 26 mm valves required post-dilatation; 12% (4/33) of 29 mm valves required post-dilatation with incremental volume (1 to 2 mL). After post-dilatation, 100% of valves showed reduced AI with either trace or no leak. 5 of the 261 TAVR procedures (1.9%) suffered significant complications, including 3 emergent ECMO placements and 3 pericardiocentesis procedures. These valves were deployed at nominal volume and were within indicated ranges for their respective annular areas (three 23 mm valves and two 26 mm valves). None were post-dilated.

**Conclusion:** Our current sizing strategy for S3 device on TAVI seems to be able to effectively eliminate significant the degree of post implant aortic regurgitation. Longer echocardiographic follow up will be needed to confirm our initial post procedural finding.
Prematriculant Students
ABSTRACT

The use of deubiquitinating enzymes to enhance PARP inhibitor cancer treatments on BRCA1-negative ovarian cancer cells

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Sponsored by: Jianping Jin, Ph.D. Department of Biochemistry and Molecular Biology
Supported by: 
Key Words: PARP inhibitor cancer treatments.

The ubiquitin proteasome pathway is responsible for protein catabolism in animal cells. This process can be divided into several steps. The first step is the initial tagging of proteins to be degraded and the conjugation of several ubiquitin enzymes. Following is the degradation of such proteins through a proteasome and helper catalytic molecules. The ubiquitin enzymes, E1 and E2, enable the conjugation of ubiquitin molecules through adenylation and thioesterification of the c-terminal residues of ubiquitin. This conjugation leads to chain linkages between ubiquitin molecules as well as with the target proteins. Recent studies have discovered that ubiquitination does not always end with complete degradation of a target protein. Often ubiquitin and subsequent enzymes can be responsible for protein modification. Ubiquitination can also repair DNA by regulating the DNA damage response pathway. However specific deubiquitination enzymes known as DUBs can reverse ubiquitin conjugation. These molecules have the ability to edit and remove ubiquitination and thereby also regulate the DNA damage response system. It has been found that an overexpression of DUBs makes cancer cells resistant to therapy such as radiation and chemotherapy. This is correlated with lower recovery and survival of cancer patients. Two candidate molecules, PC-68 and PC-69, that were isolated from plants, have recently been found to arrest mammalian cells at G1 phase and enhance protein ubiquitination. These two compounds were paired, at low concentrations, with Olaparib, a Parp inhibitor and FDA-approved cancer drug that kills BRCA1-negative ovarian cancer cells. The results showed that this treatment did not affect normal cell cycle or proliferation, but did successfully kill cancer cells. We hypothesize that PC-68 and PC-69 molecules are DUB inhibitors and therefore inhibit DNA damage-induced BRCA1 foci formation and block BRCA1 function.

To test this hypothesis, dozens of DUB proteins, whose functions have been linked to DNA repair pathway and homologous recombination, will be expressed and purified with a baculovirus and insect cell system. They will then be treated with the two candidate molecules. Simple fluorescent assay will be used to detect deubiquitinating enzyme activity. Positive and negative controls will be used to determine the baseline DUB protein levels. If DUB-detector analysis shows a reduction of deubiquitinating enzyme activity then we can conclude that the two candidate molecules are DUBs inhibitors. Further experiments will be designed to tests optimal levels of PC-68 and PC-69 with PARP inhibitor treatments to improve current ovarian cancer therapy.
ABSTRACT

Immunohistochemical Classification of the Repeat Weight Drop Injury Model for Repeated Concussions

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Sponsored by:  Pramod Dash, Ph.D., Department of Neurobiology and Anatomy
Supported by:  Mission Connect/TIRR Foundation
Key Words:  repeat concussion, traumatic brain injury, repeat weight drop injury

Concussions, also referred to as mild traumatic brain injury (mTBI), are common in the United States. They can cause several acute neurological and cognitive impairments, including balance problems, headaches, vomiting, memory deficits, and complex learning deficits, among other symptoms. The consequences of repeated mTBI have recently entered the public eye following the passing of several notable professional athletes that exhibited significant cognitive deficits towards the ends of their lives. Recent studies based on pathologies seen in these athletes have indicated that repeated concussive and sub-concussive injuries can lead to the development of chronic traumatic encephalopathy (CTE). Thus, understanding the mechanisms that cause impairment following repeated mTBI is an important endeavor. We set out to create and characterize a mouse model of mTBI that replicates the hallmarks of mTBI found in humans: acute neurological disturbances, axonal damage and neuroinflammation that occur in the absence of overt brain damage. To this end, we devised a repeat closed head injury model that uses a remotely operated electromagnet to drop a 9.8 gram bar from a height of 1.2 meters onto the dorsal surface of an anesthetized mouse’s skull. The injury was repeated four times (once every 24 hours), and animals were transcardially perfused with paraformaldehyde two hours after the final injury for immunohistochemical evaluation of cell damage markers. At the gross level, the injured brains appeared anatomically normal with no overt brain damage. These mice were found to have hippocampal dysfunction as indicated by an inability to learn the Morris water maze. Based on this result, we focused our analysis on the hippocampus, a structure in the temporal lobe that is critical for learning and memory. I observed that although there was no overt neuronal loss or dendritic damage, the patterns of GFAP, Iba1, and myeloperoxidase expression indicated that there was a mild neuroinflammatory response. These findings indicate that our repeat closed head injury model possesses some features that are consistent with repeated concussive injuries in humans. The advantage of our model is its simplicity, as the magnitude of the injury can be altered by adjusting the height and weight of the object being dropped. This foundational study has provided a baseline magnitude of injury that will help to direct future studies.
ABSTRACT

Hypoglycemia in Confirmed Mitochondrial Disease

MICHAEL B. BAGG  McGovern Medical School at UTHealth  Class of 2021

Sponsored by:  David F. Rodriguez-Buritica M.D., Department of Pediatrics
Supported by:  Summer Research Program
Key Words:  Mitochondrial Disease, Hypoglycemia, Electron Transport Chain

Background: Mitochondrial disease refers to a group of medical conditions associated with ETC dysfunction and mitochondrial dysfunction. It is often associated with endocrine disorders such as diabetes mellitus, hyper- and hypothyroidism, and hypoparathyroidism. Hypoglycemia and mitochondrial disease have not been extensively studied. It is speculated that hypoglycemia co-existence is rare and its presence can likely be attributed to adrenal insufficiency or human growth hormone deficiency. Our goal was to retrospectively document episodes of hypoglycemia in patients with confirmed mitochondrial disease, as defined by the Walker criteria.

Methods: The study was performed at McGovern Medical School. Study was approved by the McGovern School of Medicine Internal Review Board. Medical Records were reviewed on 134 patients at Memorial Hermann hospital with confirmed mitochondrial disease as defined by the Walker criteria. Records were reviewed for hypoglycemia, date of hypoglycemia, age, nuclear DNA mutations, mitochondrial DNA mutations, and for mitochondrial syndromes. Hypoglycemia was defined as a blood glucose level below 70 mg/dl. Neonatal hypoglycemia was excluded from the study. Cases were classified as single hypoglycemia and multiple hypoglycemia episodes.

Results: 48 patients were identified to have hypoglycemia out of 134 reviewed patients. 20 of the hypoglycemic patients had an associated DNA mutation. 16 patients of the 134 total patients had a depletion syndrome and 11 of those patients had at least an instance of hypoglycemia. 24 patients had multiple hypoglycemic events.

Conclusions: Prior to this study there was a lack of data on the presence of hypoglycemia in individuals with mitochondrial disease. It was anticipated that there would likely be a few cases since endocrine issues are commonly associated with mitochondrial disease, but it was not predicted that 35% of study participants would present with at least one hypoglycemic event. This was a pilot study on the subject. It had limitations associated with a retrospective analysis. Further research should be established to confirm our findings and to evaluate on additional co-existing conditions such as adrenal insufficiency or growth hormone deficiency that could be the cause of hypoglycemia in association with mitochondrial disease. It is also possible that additional mechanisms due to mitochondrial dysfunction explain the rate of hypoglycemia observed in our cohort of patients.
ABSTRACT
Pediatric Surgery: Surgical Safety Checklist

RIGO GUTIERREZ McGovern Medical School Class of 2021

Sponsored by: KuoJen Tsao, MD, Department of Pediatric Surgery
Supported by: KuoJen Tsao, MD, Department of Pediatric Surgery, McGovern Medical School
Key Words: Quality Assurance, Pediatric Surgery

For the Summer Research Program (SRP) I worked in the pediatric surgery department at Memorial Hermann Hospital for eight weeks. My team and I focused on surgical safety checklist (SSC) adherence and how it related to patient engagement and surgical outcomes. The SSC allowed for better communication between the surgical team, as well as an added layer of protection of the patient and accountability of the health care providers. We observed pediatric surgeries of specialties such as neurosurgery, plastic surgery, urology, ear-nose-throat (ENT) surgery, cardiothoracic surgery, and general surgery. The SSC consisted of a pre-induction, pre-surgical, and debriefing. We used the different checklist items in order to examine different variables to see if increased parent engagement during the pre-induction phase had any correlation with SSC adherence. We also searched for correlations between adherence to SSC and patient outcomes. My team and I also worked on various chart reviews in order to identify places where quality improvement could increase in the work place. We used statistics and programs like Excel and RStudio in order to analyze the data that was collected.
Effect of Peptide Functionality on Hyaluronan Scaffold Degradation
Rates and Human Induced Pluripotent Stem Cell Proliferation

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Sponsored by: Laura Smith Callahan, PhD, Department of Neurosurgery and the Center for Stem Cell and Regenerative Medicine
Supported by: Laura Smith Callahan, PhD, Department of Neurosurgery and the Center for Stem Cell and Regenerative Medicine; The University of Texas Health Science Center at Houston Medical School – Office of the Dean
Key Words: Peptide functionalization, human induced pluripotent stem cells, scaffolds, tissue engineering, degradation, cell proliferation

BACKGROUND: Spinal cord injury affects roughly 270,000 Americans. There are currently no existing treatments that can restore function to patients, although a hyaluronan (HA) scaffold-based stem cell therapy approach shows promise. Scaffolds provide a matrix for cell regeneration in neural lesions. HA can be functionalized with chemical groups to promote human induced pluripotent stem cell derived neural stem cell differentiation, axon extension, cell signaling, and material degradation. We compared the effect of peptide functionalization on scaffold degradation and cell proliferation to that of a baseline HA formulation to determine how long a scaffold could theoretically survive in vivo and whether such functionalization would provide a countermeasure to unchecked cell growth.

METHODS: HA scaffolds were prepared from three formulations: baseline (dif HA), IKVAV and LRE peptide moieties (pep HA), and pep HA with a third matrix metalloproteinase-cleavable peptide (mmp HA), which is necessary for axon extension. Hyaluronidase and collagenase experiments were run to examine scaffold degradation. Uric acid production was measured using a modified carbazole approach. Cell proliferation was measured using a Pico Green assay for DNA quantification. Doubling times for each gel formulation/media combination were calculated.

RESULTS: The hyaluronidase experiment showed significant differences in HA degradation between dif HA and pep HA starting at 48 hours, while all formulations diverged beginning at 96 hours. The collagenase degradation showed dif HA maintaining mass and mmp HA degrading significantly starting at 48 hours. The cell proliferation experiment did not show significance until 14 days, though pep Ha standard deviations were lower in both formulations throughout. Doubling times for each of the four combinations were not significant.

DISCUSSION: The hyaluronidase degradation results indicate that HA scaffolds will degrade more rapidly if functionalized with peptide. Cell doubling times indicate that functionalization does not affect cell growth rate, though experiments extending toward much longer time points may change this result. The cell proliferation results themselves imply that functionalization makes a difference only when combined with differentiation.
media, as pep HA growth in differentiation media was significantly lower than both dif 
HA media results.
**ABSTRACT**

Role of Industry Funding in Academic Dermatology

**KYLE LAUCK**  
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*Class of 2021*

**Sponsored by:** Adelaide A Hebert, MD, Department of Dermatology and Pediatrics

**Key Words:** Funding, Dermatology, Industry, Research

Since 2003, the NIH Budget for research grants has diminished. As a result more academic physicians are turning to pharmaceutical and medical device companies for funding. The aim of this project was to examine the relationship between private industry funding in Dermatology and the relative scholarly impact created by investigators who received this funding.

The objective of this study was to compare the impact of the h-index, a weighted index of academic productivity, to the amount of industry research funding received by colleagues. Using Dermatology department websites, the Center for Medicare and Medicaid Services (CMS) open payments database, and the Scopus database, bibliometric data on Academic Dermatologists were collected. The 2-sided unpaired t-test was used for continuous variables.

Of 1,737 Academic Dermatologists, 209 received industry funding for the purposes of research with a median research payment total of $58,238.38. Academic Dermatologists who received any industry funding for the purposes of research had a higher h-index (Funded h-index: 20.74, non-funded h-index: 9.68, p<0.0001). This result was seen across the different academic ranks: Assistant Professor (Funded h-index: 8, non-funded h-index: 4.32, p<0.0001), Associate Professor (Funded h-index: 13.57, non-funded h-index: 10.07, p<0.0001), and Professor (Funded h-index: 32.81, non-funded h-index: 24.07, p=0.0008). Among gender the h-index was significantly higher for those who received industry funding for the purposes of research within both males (Funded h-index: 24.48, non-funded h-index: 12.85, p<0.0001) and females (Funded h-index: 15.06, non-funded h-index: 6.4, p<0.0001).

Our study had several limitations including incomplete information with respect to some departmental websites as well as both databases in terms of being up to date. The limited time CMS data has been documented also presented potential limitations.

Industry funding in Academic Dermatology is correlated with a higher scholarly impact. This trend was seen across academic rank and sex. Given the continued budget limitations of the NIH, industry funding is more likely to play an important role in Academic Dermatology. What remains to be seen is whether this funding caused the increase in scholarly impact, or if the high scholarly impact itself was the factor which attracted the increased level of funding. With the CMS database still young, time and further research may elucidate this question.
ABSTRACT

Leukocyte Elevation after Subarachnoid Hemorrhage

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Sponsored by:  Dr. H. Alex Choi, MD, Department of Neurosurgery  
Supported by:  Dr. Jude Javarraj  
Key Words:  Subarachnoid Hemorrhage, Leukocytes, Delayed Cerebral Ischemia

Subarachnoid Hemorrhage (SAH) is caused by the rupture of a cerebral aneurysm and the hemorrhaging of blood into the subarachnoid space. It affects 30,000 Americans annually affecting them with severe physical and/or and cognitive disabilities. After 3-14 days of ICU admission, 20-25% of SAH patients develop a serious secondary complication called delayed cerebral ischemia (DCI) which is characterized by narrowing of cerebral blood vessels resulting in cerebral ischemia that irreversibly worsens patient’s condition. The underlying etiology of DCI is unclear, but there is increasing evidence that uncontrolled inflammation may play a central role. In this study we explored the role of early inflammation and its association with the patient’s clinical status, DCI and patient outcomes. We hypothesize that increased peripheral inflammation, measured by the white blood cells (WBC), is associated with poor clinical status, DCI and outcomes. This is a retrospective single center study of 480 patients admitted to the neuroscience intensive care unit at Memorial Herman hospital. Patients were assessed for clinical status using the Hunt-Hess (HH) grade (a gradient score from 1 to 5, with ‘1’ being good and ‘5’ being the worst), DCI, and their functional outcomes at discharge using the modified rankin (mRS) score (a gradient score from 1 to 6 scale with ‘1’ being good and ‘6’ being dead). Patients were dichotomized into HH≤3 vs HH≥4, DCI vs no-DCI, mRS≤3 and mRS≥4. WBC differentials beginning from the day of admission to discharge was obtained from the EMR. Statistical tests included student’s t-test, a Chi-square test, and a multivariate logistic regression (MLR). In all SAH patients, WBC, monocyte, and neutrophil levels decreased until day 4 and then steadily increased until discharge. Monocyte levels peaked at day 7, then began to decrease. WBC, monocyte, and neutrophil levels were significantly higher at admission in patients with high HH grade (16.66 ±0.6 vs 13.21 ±0.34, p<0.05), DCI (15.05 ±0.7 vs 13.99 ±0.37, p <0.05) and poor mRS (16 ±0.62 vs 13.13 ±0.34, p<0.05). The difference in levels remained significant throughout the remainder of patient stay. MLR analysis determined that monocyte and neutrophil levels were independently associated with DCI. Also, WBC, monocyte, and neutrophil levels were independently associated with mRS after accounting for possible confounders including age and HH. Poor clinical status, DCI and worse outcomes are associated with early elevation of WBC levels. WBC cells could be important prognostic markers of DCI and poor outcomes.
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Undergraduate Students
ABSTRACT

HTN Expression in Allergic Fungal Rhinosinusitis

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Class of 2019

Sponsored by: Amber Luong, MD, PhD, Department of Otorhinolaryngology-Head & Neck Surgery
Supported by: American Academy of Otolaryngology- Head and Neck Surgery Research Grant
Key Words: Chronic rhinosinusitis, gene expression, histatin

Background: Chronic rhinosinusitis (CRS) is an inflammation of the sinuses lasting more than 12 weeks. Clinical subtypes of CRS include allergic fungal rhinosinusitis (AFRS), chronic rhinosinusitis with polyps (CRSwNP), and chronic rhinosinusitis without polyps (CRSsNP). AFRS is currently considered a subtype of CRSwNP; however, there is debate whether AFRS can be considered a separate disease from CRS altogether. HTN1 and HTN3 are a family of genes that encode histatins, antimicrobial proteins. Histatin expression has not previously been studied in sinus mucosa.

Methods: Sinus tissue and blood samples from consenting patients undergoing endoscopic sinus surgery were collected. Patients were categorized into AFRS, CRSwNP, CRSsNP, or HC (healthy control) subtypes. Following tissue culture, RNA was extracted. Real-time PCR quantified expression of HTN1 and HTN3 in tissue samples and cell fractions, using beta-actin as the reference gene.

Results: HTN1 and HTN3 expression are decreased in AFRS patients as compared to CRSwNP patients. PCR of additional patient samples is currently underway.

Conclusion: PCR results confirm initial microarray findings distinguishing AFRS from CRSwNP on a molecular basis, specifically the altered expression of the histatin protein. Our findings facilitate further research into the mechanism behind altered histatin expression in AFRS. This research further advocates for the classification of CRS into disease endotypes, rather than clinical subtypes; this approach has already been successfully applied to asthma. This is significant clinically, as novel treatments targeting specific endotypes can be developed to improve patient outcomes.
ABSTRACT
The Role of Transportin IMB-2 in Infection

ALI AL HATEM  University of Houston – Main Campus  Class of 2019

Sponsored by: Ransome van der Hoeven, PhD, Department of Diagnostic & Biomedical Sciences, UT School of Dentistry
Supported by: Ransome van der Hoeven, PhD
Key Words: Streptococcus gordonii, Caenorhabditis elegans, and hydrogen peroxide.

Background: The mitis group streptococci such as Streptococcus gordonii, S. mitis and S. oralis are ubiquitous microorganisms that colonizes the human oropharynx. In immunocompromised hosts, these organisms are important opportunistic pathogens and they have shown to cause a wide range of infectious complications. However, despite the clinical significances of these infections, the mechanisms of pathogenesis are poorly understood. Using the nematode Caenorhabditis elegans, hydrogen peroxide (H₂O₂) produced by these organisms has been identified as a virulence factor. C. elegans is an excellent system to study mechanisms of pathogenicity and stress responses. As part of its defense against oxidative stress, the insulin signaling pathway regulates the expression of genes involved in antioxidant stress-response. This pathway consists of a receptor DAF-2, the PI3-kinase signaling cascade culminating with the forkhead box O (FOXO/DAF-16) transcription factor. The activity of DAF-16 is largely regulated through nucleo-cytoplasmic shuttling. In addition to the insulin-dependent signaling, the Reactive Oxygen Species (ROS)-dependent signaling axis controls nucleo-cytoplasmic shuttling of DAF-16. A recent study demonstrated ROS, through cysteine oxidation regulates the nuclear import of FOXO4 by forming a heterodimer with the protein karyopherin TNPO1 in human cell lines. Further, the authors confirmed the nuclear localization of DAF-16 mediated by a TNPO1 homologue IMB-2 was observed in C. elegans in response to paraquat (a superoxide generator). No studies were conducted to ascertain the role of IMB-2 during infection.

Hypothesis: Therefore, we hypothesize IMB-2 will recruit DAF-16 to the nucleus, thereby activating the expression of ROS scavenging enzymes in response to H₂O₂ produced by S. gordonii.

Methods: To test our hypothesis, we determined the survival of imb-2, daf-16 and daf-2 knockdown worms relative to the vector control worms on S. gordonii. Using an intestinal specific RNAi knockdown strain vha6p::sid-1, we further determined the survival of imb-2, daf-16 and daf-2 knockdown worms relative to the vector control worms. Finally, using confocal microscopy, we observed the nuclear localization of DAF-16 in a transgenic worm expressing DAF-16 fused to GFP when imb-2 and daf-16 were knockdown relative to the vector control in response to the infection.

Results: The survival of the imb-2 and daf-16 knockdown worms was significantly less compared to the vector control treated worms on S. gordonii. More importantly, the knockdown of imb-2 and daf-16 within the intestine caused the worms to succumb to the pathogen more rapidly when compared to the vector control treated worms. In addition, compared to the vector control we
observed significant loss of localization of DAF-16::GFP in *imb-2* and *daf-16* knockdown worms during infection.

**Conclusion:** Our data suggests IMB-2 is required for the survival of the worms and is important for the translocation of DAF-16 in response to the H$_2$O$_2$ produced by *S. gordonii*. 
ABSTRACT

The role of AgrB₂D₂ locus in hypervirulent strains of Clostridium difficile

CLAUDE ALBRITTON
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Background: Expression of the agrB₂D₂ locus may be a significant factor in the biology of Clostridium difficile, but its role is unknown. Prior studies have shown that its agrB₁D₁ homologue plays a vital role in toxin production. The goal of this project was to determine the role of the agrB₂D₂ locus in hypervirulent C. difficile strain R20291 based on the hypothesis that this locus may be play a role in pathogenesis.

Methods: Sporulation and biofilm formation were examined. To test for sporulation, overnight cultures of the agrB₂D₂ mutant were heated for 30 minutes at 65°C to kill vegetative cells, plated on selective plates and incubated under anaerobic conditions for three days. Colony-forming units were calculated based on the yield of each plate. For the biofilm test, the mutants were incubated in 24-well plates under anaerobic conditions for six days. The biofilms were washed with phosphate-buffered saline, stained with crystal violet dye, and extracted with ethanol. The ethanol-extracted dye was analyzed using a spectrophotometer.

Results: The results indicated that the agrB₂D₂ mutants were defective in spore formation, as the number of colony-forming units obtained from the mutants was significantly lower than that from the wild type. The amount of biofilm obtained from the agrB₂D₂ mutants was also significantly lower than that of the wild type.

Discussion: Our results support the hypothesis that the agrB₂D₂ locus may play a role in C. difficile pathogenesis. However, further analyses such as complementation of the mutants are necessary to confirm this initial observation. Other virulence factors such as toxin production and motility may also need to be evaluated to fully understand the role of the C. difficile agrB₂D₂ locus.
ABSTRACT

Re-thinking periapical inflammation. The role of immune cells in determining the outcome of periapical pathologies

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Class of 2019

Sponsored by:  Flavia S. Lakschevitz DDS, Ph.D., Periodontics & Dental Hygiene  
Supported by:  Endodontics Department of UTSD. Dr. Renato Silva start-up funds.

Key Words:  Apical periodontitis, neutrophils, NETs

Background: Neutrophils (PMN) are the most abundant white blood cells and key components of the innate immune response. NET formation or NETosis represents an important antimicrobial mechanism of the innate immune system. Periapical diseases are inflammatory diseases located in the periradicular tissues in response to a bacterial insult to the root canal system. Neutrophil hyperactivity is based on studies that demonstrate that NET release is dependent on reactive oxygen species (ROS) production, which is increased in patients with chronic periodontitis. Only about 30% of neutrophils form NETs, the reason why some neutrophils form this mechanism, and others do not is still unknown. In our study we focused on the role of NETs in periapical periodontitis, specifically periapical cysts and granulomas. The goal of our study was to investigate the role of neutrophils and their release of NETs to have a better understanding of potential neutrophil phenotype and periapical periodontitis disease outcome.

Methods: Sections from 10 acute periapical granulomas, 10 chronic periapical granulomas, and 10 periapical cysts were stained with H&E and immunofluorescence using anti- myeloperoxidase (MPO) and anti-neutrophil elastase (NE), primary antibodies. Slides were also stained with DAPI to detect NET formation. NET positive cells were identified by cells that produced extracellular, decondensed DNA in fibers or in a web-like shape that would co-localized with NE. PMN were counted with ImageJ software based on nuclear morphology to obtain an average of PMN infiltration present in periapical lesions.

Results: H&E counted slides of acute granulomas, chronic granulomas and cysts provided an average PMN count of 49.19 (±30.20), 2.18 (±2.05) and 11.43 (±7.03), respectively. The ratio of PMNs to Lymphocytes in acute granulomas was 1.8, while in cysts were 0.1. The number of PMNs was significantly higher in acute granulomas when compared to cysts. Since we are interested in exploring the idea that neutrophil NET formation will play a role in determining periapical disease outcome, we will identify the PMN phenotypes using immunofluorescence techniques. We are currently in the process of quantification of the NET formation and statistical analysis.

Conclusion: Based on the obtained results we were able to identify and quantify immune cells in three major periapical pathologies and as expected, an exuberant presence of neutrophils was identified in acute granulomas. We anticipate that increased NET formation will be associated with a more aggressive disease profile.
ABSTRACT

The Pathway of IRF6 using Salivary Gland and Pancreas

Sameer Bilal

University of Houston  Class of 2018

Supported by: Walid D. Fakhouri, MSc, PhD, UTHealth School of Dentistry, Department of Diagnostic and Biomedical Sciences; UT School of Dentistry at Houston Research Office

Key Words: IRF6, transcription factor, salivary glands, pancreas, histology, immunohistochemistry staining, cleft lip and palate, Van der Woude Syndrome, Popliteal Pterygium Syndrome, Matrix Metalloproteinase, Aquaporin

Background: Interferon regulatory factor 6 (IRF6) is a member of the IRF family of transcription factors. IRF6 encodes for transcription factors that regulates expression of interferons and other signaling proteins that are critical for proper immune functions and biological processes during craniofacial development. Although the regulative roles of IRF6 has been confirmed in epithelial, immune, and erythropoiesis pathways, its mechanism of regulation in osteoblastic differentiation remains largely unknown. Mutations in IRF6 cause Van der Woude (VWS) and Popliteal Pterygium Syndromes (PPS) and contribute to the risk of cleft lip and palate (CLP). Irf6 null mice are born with abnormal craniofacial structures as compared to mice with Irf6 and they show a loss of mucous acini in salivary glands and large spatial arrangement between acinar cells in pancreas. The aim of this project was to determine the regulatory pathway of Irf6 by detecting the level of potential interacting and downstream targets using IHC. The expression of Matrix Metalloproteinase 2 (MMP2), MMP3 and Aquaporin 5 (AQP5) was detected in salivary gland tissues and pancreas.

Methods: We used a microtome to get fine sections of the salivary gland and pancreas samples to be used in our study. We performed H&E and Immunohistochemistry (IHC) staining for the antibodies MMP2, MMP3 and AQP5 on the wild type and IRF6 null samples obtained from sectioning. Ages of the specimens used were E15.5, E17.5 and PO.

Results: H&E staining showed a clear difference in terms of organization and cell types and helped us differentiate between wild type and IRF6 null samples. The salivary glands in Irf6 null mice were disorganized and had almost no mucous acinar cells relative to the wild type. In Irf6 null pancreas, abnormal morphology and disorganization of cells was observed. The nuclei appeared to be on the apex as compared to the wild type pancreas where it was generally in the center of the cytosol. The antibodies tested were expressed in the cytosol in wild type pancreas and had almost no expression in mutant cells. They were expressed only in the acini for wild type salivary glands and were not expressed in mutant cells.

Conclusion: Our findings indicate that Irf6 is critical in the development of salivary glands and pancreas. These results suggest that DNA variations in IRF6 contribute to the risk of salivary gland and pancreatic disorders in humans. Knowing that MMP2, MMP3 and AQP5 were expressed in the wild type cells, it will suggest a regulatory role of IRF6 in extra-cellular matrix. Our future goals are to figure out more branches in the pathway for IRF6 and translate these findings into the clinic to identify genetic risk factors in patients with salivary gland and pancreas disorders.
ABSTRACT
Applications of Blender in Science

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Sponsored by: Jun Liu, PhD, Pathology
Key Words: Blender, Borrelia, Salmonella, science, communication

Understanding biological processes is necessary for developing medicine, and visualization is the best method to do this. Blender assists with mechanism visualization by creating 3D objects. Since Blender is an open-source software written in Python, custom software tools are typically created on an as-needed basis to assist with the modeling of data. In this review, I will explain how Blender has benefitted the scientific community already, is being used in Dr. Liu’s lab, and how easy Blender is to learn. Serial electron microscopy images have been processed with the NeuroMorph software for Blender to reconstruct the morphology of neurons and other cell types (Jorstad & Nigro, 2014). Fluorescent microscopy images have been processed with the MCell software for Blender to generate spatially realistic models of cell processes (Kerr, Rex A. et al., 2008). In Dr. Liu’s lab, we are using Blender to visualize the mechanisms of Borrelia motility and Salmonella infection. Data on the dimensions of a wild-type and mutant Borrellia cell were collected with cryo-electron tomography, and an arbitrary scale was used to convert the measurements collected to Blender Units to manually build each model. Due to computing power limitations at the time, only pictures could be generated of these models. Using a similar procedure, a Salmonella model was manually constructed, but since this model required less computing power, an animation was able to be generated. With the completeness of Blender’s documentation, the plethora of free online tutorials, and large community of Blender users, it should not take long to learn Blender.
ABSTRACT

Assessment of Immunopathology to Mycobacterial Trehalose 6,6’-dimycolate in C57BL/6 and C3Heb/FeJ Mice.
Byerly, C.D., Hwang, S-A., and Actor, J.K.

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Class of 2018

Sponsored by: Jeffrey K. Actor, PhD, Pathology and Laboratory Medicine
Supported by: Jeffrey K. Actor, PhD, Professor
Key Words: Tuberculosis, trehalose 6,6’-dimycolate, Granuloma, Immunopathology

*Mycobacterium tuberculosis* (MTB) is a pathogen that infects and kills millions yearly. The mycobacterium’s cell wall has the glycolipid trehalose 6,6’-dimycolate (TDM), which is used to model MTB induced inflammation and granuloma formation in mice. The purpose of this experiment was to study and compare TDM effects in C57BL/6 (C57) and C3Heb/FeJ (C3H) mice, to better understand the cytokine responses contributing to cellular phenotypes involved in development of the granuloma, a common MTB pathology. C57 and C3H mice were intravenously injected with 25 µg of TDM. Mouse lungs were assessed for general lung inflammation (lung weight index; LWI) and lung pathology (histology), as well as for the production of proinflammatory cytokines and chemokines over the course of 10 days post introduction of TDM. Lungs were also assessed for infiltrating cell phenotypes by flow cytometric analysis at times of expected peak granulomatous response. Comparing both strains, the C57 and C3H LWI was approximately the same at day zero, but C57 mice had a slightly higher LWI at days 3, 7, and 10. Lung histology revealed granuloma formation beginning at day 3 in both C57 and C3H mice. At days 7 and 10, granuloma pathology in C57 mice was dramatically more pronounced and occupied more lung tissue area than in C3H mice. ELISA was used to analyze immune mediators in the lung. Overall, higher levels of cytokines were present in C57 lungs than in C3H lungs, correlating well with the differences in the degree of granuloma pathology observed. Lungs from C3H mice had significantly less IL-1β at days 7 and 10 compared to C57 mice. The amount of T-cells, NKT cells and macrophages was measured using flow cytometry. Overall, C57 mice had a higher percent of these infiltrating populations, with significant presence of NK1.1 positive T cells. These results suggest that the production of IL-1β and presence of NKT cells may influence the aggression of the TDM granuloma response.
Abstract
The Role of BMPR2 in Lung Fibrosis and Pulmonary Hypertension

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Class of 2018

Sponsored by:  Dr. Harry Karmouty-Quintana Ph.D.
Supported by:  Genentech Grant: G-45857
Key Words:  Idiopathic Pulmonary Fibrosis, Pulmonary Hypertension, BMPR2, CD206, COL1A1, Bleomycin

Background:  Idiopathic Pulmonary Fibrosis (IPF) is a fatal disease in which fibrotic proteins such as collagens and fibronectin that form the lung extracellular matrix are overexpressed. This overexpression in lung tissue causes thickening and stiffness, causing difficulty breathing due to obliteration of the alveolar surface. Studies show that average patient survival is 5 years. There are a limited number of treatments for IPF, which is why it is important to understand the cellular pathways contributing to the development of this disease. Recent studies by our group suggest that macrophages may be involved in promoting the fibrotic response in the lungs. The aim of the study was to evaluate whether depletion of Bone Morphogenic Protein Receptor 2 (BMPR2) in macrophages affected the development of lung fibrosis. BMPR2 is a member of the Transforming Growth Factor (TGF-B) superfamily which promotes cell proliferation. Under normal conditions, BMPR2 associates with the ligands SMAD 1, 5, and 8 that bind to the complex which thus inhibits activity of TGF-B. Loss of function of BMPR2 leads to proliferation, vascular remodeling, and development of PH. Other proteins involved in fibrosis are COL1A1, a collagen inducer, and CD206, a protein found on macrophages. However, how macrophage BMPR2 expression modulates fibrosis is not known.

Hypothesis:  Loss of BMPR2 leads to worsening lung fibrosis.

Methods:  BMPR2 Flox Lysm-Cre mice were injected intraperitoneal (i.p.) twice a week for 33 days with Bleomycin. Organ harvests were conducted after the last treatment. The lungs were frozen in liquid nitrogen for in western blot analysis and formalin fixed for αSMA staining to determine levels of key proteins and fibrosis.

Results:  From the αSMA stains, we conclude that there is more fibrosis expressed in the diseased lungs treated with bleomycin compared to normal lungs. From western blot analysis, we found that BMPR2 depletion tracks with fibrosis. We also report increased levels of COL1A1 in Bleo Lysm-Cre mice and decreased expression of Bleo BMPR2 Lysm-Cre mice. Similar results were seen with CD206 expression increase in Bleo Lysm-Cre mice and decreased in BMPR2 Bleo Lysm-Cre mice.

Conclusions:  Our results show a depletion in BMPR2 leads to worsening fibrosis. Now that we have seen a depletion of BMPR2 in the lung in the bleomycin model, we can assess the temporal expression of these proteins and how this correlates with disease progression. These studies shed light on the molecular mechanisms involved in cardio and pulmonary diseases, which brings us closer to developing better treatments.
Catherine Chang  McGovern Medical School  Class of 2020
Miranda Dam  University of Wisconsin-Madison  Class of 2019

ABSTRACT
Cold and Exercise Exposure Stimulates Lipolysis through Upregulation of Adipose-Derived VEGF-A via Activation of Sympathetic Nervous System (SNS)

Obesity is a major risk factor for many epidemic diseases including type 2 diabetes and cardiovascular disease (CVD). During obesity development, vascularization by angiogenesis in adipose tissue cannot keep the pace with the rapid speed of fat mass expansion. This may further cause local hypoxia, fibrosis, macrophage accumulation and inflammation which ultimately lead to systemic insulin resistance, the hallmark of type 2 diabetes. Importantly, we recently found that overexpression of a key angiogenetic factor VEGF-A in transgenic mice dramatically improves the vascularization in the obese adipose tissue, which hence protects transgenic mice not only against high-fat diet (HFD)-induced obesity but also insulin resistance. To observe potential inducible effects on VEGF-A, we placed mice under cold and exercise conditions, known methods associated with weight loss. We observed a more multilocular appearance of white adipocytes and significant upregulation of UCP-1, confirming a browning effect on the subcutaneous white adipose tissue (sWAT). These browning effects include increased energy expenditure and metabolic improvement in dissipating excess energy as heat. Furthermore, we found a massive upregulation of VEGF-A stimulating angiogenesis. To potentially mimic the cold and exercise exposure conditions, we used a doxycycline (Dox) inducible adipose tissue specific VEGF-A overexpression mouse model. In these transgenic mice we found that local overexpression of VEGF-A stimulates lipolysis in adipose tissue by upregulating hormone sensitive lipase (HSL) expression and enhancing its phosphorylation levels in adipocytes. As the result, the VEGF-A transgenic mice exhibited smaller adipocytes and reduced total fat mass shortly after VEGF-A induction. Intriguingly, the local norepinephrine (NE) levels in adipose tissue were dramatically increased in the transgenic mice. Immunofluorescent staining (IF) with anti-tyrosine hydroxylase (TH) antibody further showed higher density of neurons innervated in the adipose tissue of the transgenic mice. These findings clearly demonstrate that the sympathetic tone activated by VEGF-A plays a key role in adipose tissue lipolysis, which eventually leads to enhanced energy expenditure. These studies show that cold and exercise conditions stimulating the upregulation of VEGF-A may be potential targets for treating obesity.
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ABSTRACT

Interactions between E. coli division proteins FtsA and FtsN – probing the 1c subdomain of FtsA

ERICA DUNCAN         Del Mar College        Class of 2017

Sponsored by:    William Margolin, PhD, Department of Microbiology and Molecular Genetics
Supported by:      The Gillson Longenbaugh Foundation and The University of Texas MD Anderson Cancer Center UTHHealth Graduate School of Biomedical Sciences.
Key Words:        E. coli, cell division, FtsA, FtsN

Cell division is a critical biological process in Escherichia coli and it is imperative that it is accomplished precisely. Within the E. coli cell, the subcomplex controlling cell division is called the divisome. The divisome contains 12 essential division proteins and numerous other proteins whose main primary functions remain unknown. The essential cell division protein FtsA assists in anchoring FtsZ to the membrane and recruiting the downstream cell division proteins to the septal ring. FtsN, a late division protein, which activates septal peptidoglycan synthesis and constriction of the cell, is known to interact with FtsA. It has been shown that FtsN binds to residues within the FtsA 1c subdomain, comprised of 77 amino acids, but which specific amino acids are responsible for this interaction is not known. By using a ‘cut and paste’ method of mutagenesis, we targeted five potential FtsA residues -- 127, 128, 129, 130, and 131. A series of deletions and alanine substitutions were examined using bacterial two-hybrid analysis to determine if FtsA-FtsN interactions were interrupted by these mutations. The preliminary results suggest that residues 127 and 128 are involved in this important interaction. We will continue to probe this interaction with single amino acid substitutions.
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ABSTRACT
Development of Novel Vector for Applications in Hypothalamic Neuroscience Research

BLESSING FELIX-OKOROJI
Rice University

Background: GABAergic and glutamatergic neurons in the lateral hypothalamus regulate feeding. Specifically, GABAergic activity drives consumption while glutamatergic activity produces aversion. Genetic knockout of LH GABA release produces a mild phenotype with reduced body weight and increased averseness; conversely, knockout of LH glutamatergic release does not produce obesity and only shows a mild decrease in anxiety and averseness. To expound the function of GABA and glutamate, and to identify the function of the neurons which they inhibit, we propose to convert GABAergic neurons into glutamatergic neurons. This will excite neurons which normally are inhibited. To accomplish this, we are using molecular cloning techniques to develop adeno-associated virus (AAV)-compatible plasmid construct with cre-activated expression of vglut2 and vgat, the transporters necessary for loading glutamate and GABA (respectively) into vesicles for synaptic release, as well as glutamate decarboxylase (gad1) which is necessary for synthesis of GABA from glutamate. With the conversion of these neurons from inhibitory to excitatory (and vice versa), we expect that they will exhibit the opposite behavior from normally expected with neuron activation.

Methods: Shuttle vectors carrying cDNA clones of Mus musculus gad1, vgat, and vglut2 were amplified and Pac1 and Xba1 restriction sites were added to the insert sequence. Restriction digest was then performed on each, as well as on the adeno-associated virus-compatible destination vector, pAAV-e1a-FLEX-MCS-P2A-EGFP. Then, the destination plasmid with either gad1, vgat, or vglut2 were ligated and then transformed to DH5α E. Coli cells using heat-shock technique. Each transformation was then plated on agar plates with ampicillin and stored overnight at 37°C. Afterwards, multiple colonies were chosen and grown overnight in liquid media with ampicillin at 37°C. PCR and agarose gel electrophoresis were used to confirm presence of the complete insert-destination plasmid construct. If present, restriction digest and sequencing were performed to confirm no mutations occurred.

Results: The expected band length of vgat cDNA is 1.57 kbp which was shown on agar gel after PCR and electrophoresis. The expected band length of gad1 and vglut2 are 1.8kBp and 1.7kBp, respectively. No bands on the gel corresponded to either of the two.

Conclusions: Based on gel electrophoresis, vgat was successfully inserted into the pAAV e1a-Flex-MCS-P2A-EGFP plasmid. Further testing, such as diagnostic restriction digest and sequencing needs to be conducted to confirm the presence of vgat. Gad1 and vglut2 have not been successfully inserted into the pAAV e1a-Flex P2A-EGFP plasmid. Vglut2 has been recently
re-cloned using a different set of restrictions primers, and gad1 has been re-cloned using recently made gad1 cDNA.
ABSTRACT

The transcriptional suppressor ZHX2 in Huntington’s disease

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Pomona College

Class of 2019

Sponsored by: Andrey Tsvetkov, PhD, Felix Moruno Manchon, PhD, Department of Neurobiology and Anatomy

Supported by: Hereditary Disease Foundation and the University of Texas

Key Words: Aging, Neurodegenerative Diseases, ZHX2, SK2, Huntington Disease

Background: Premature brain aging and neurodegenerative diseases are strongly associated with DNA damage and defective DNA repair processes. As neurons age, they develop deficits in their DNA repair machinery resulting in an accumulation of DNA double stranded breaks (DSBs). Consequently, increased DSBs have been identified in numerous age-related neurodegenerative diseases, such as Huntington’s Disease (HD), Alzheimer’s Disease (AD), and amyotrophic lateral sclerosis (ALS). Recent evidence suggests that modulating DNA repair is an effective strategy to mitigate DNA damage in neurodegenerative disorders. Previous research in our lab identified that sphingosine kinase 2 (SK2) is hyperactive in HD mice models and that overexpression of SK2 induces DSBs in neurons. Hence, overexpressed SK2 is neurotoxic for cultured primary neurons. We also identified a transcriptional repressor, zinc and homeobox 2 (ZHX2), as a potential binding partner of SK2. As a result, we sought to determine whether SK2 cooperates with ZHX2 in the nucleus of neurons to modulate DNA damage and repair.

Methods: Cortices (striatum, hippocampus, cerebellum) from rat embryos (E17–18) were dissected, dissociated, and plated on 24-well tissue-culture plates. Primary neurons were transfected with Lipofectamine2000 and plasmid DNA. We also used a new imaging platform, combined with imaging algorithms, to perform high-throughput longitudinal single-neuron analysis.

Results: SK2 co-immunoprecipitates with ZHX2 from the neuronal nuclear extracts. ZHX2 overexpression itself significantly increases the frequency of DSBs in neurons. Downregulation of ZHX2 significantly increases the survival of neurons that express mutant huntingtin, the protein that causes HD. Interestingly, an inhibitor of SK2 significantly increases survival of neurons that overexpress ZHX2 and decreases the number of DSBs associated with the expression of ZHX2, suggesting that SK2 and ZHX2 are a part of the same pathogenic mechanism in HD.

Conclusions: SK2 and ZHX2 are nuclear binding partners that play a role in modulating DNA damage and repair. Importantly, these results identify a new potential drug target to attenuate the accumulation of DNA damage present in a variety of neurodegenerative diseases such as HD, AD, and ALS.
ABSTRACT

Engineering of E. coli Type IV Secretion Systems for Targeted Inhibition of Intercellular Transfer

JAMIE GUILLEN  Emory University  Class of 2019

Sponsored by:  Peter J. Christie, PhD, MMG Department
Supported by:  Gillson Longenbaugh Foundation
Key Words:  Antibiotic resistance, Conjugation, Type IV Secretion System, E. coli,

Type IV secretion systems (T4SSs) assemble as translocation channels across the bacterial cell envelope and conjugative pili that mediate contacts with bacterial or eukaryotic target cells. Bacteria deploy T4SSs to deliver DNA or protein substrates to target cells. The Escherichia coli pKM101 conjugation system elaborates a T4SS and also a protein, TraC, that localizes both on the tip of the pilus and on the cell surface where it functions as an adhesin. We sought to genetically engineer TraC so it binds specific bacterial or eukaryotic receptors to enable the targeted delivery of DNA or protein effectors to specific cell types of interest. A long-term goal of this work is to use anucleated minicells of E. coli carrying a T4SS and displaying the engineered TraC surface protein that specifically binds cancer cell surface receptors for targeted T4SS-mediated delivery of toxic effectors as a novel therapeutic treatment for cancer.

As a proof-of-principle, we first sought to develop a targeted T4SS delivery system functioning to transfer DNA substrates from a bacterial donor to a specific bacterial recipient cell. To this end, we added the leucine zippers Fos or Jun to TraC. Leucine zippers (LZ) are α-helices of 30-50 amino acids in length that interact to form stable heterodimers. We tested the capacity of E. coli donors displaying TraC, TraC-Fos or TraC-Jun to E. coli recipients displaying these same proteins. We hypothesized that donors displaying TraC-Fos or –Jun would transfer conjugative plasmids at enhanced frequencies to recipients displaying TraC-Jun or –Fos, respectively, than other donor-recipient pairs. Surprisingly, contrary to our hypothesis, matings between donors and recipients both displaying TraC-Fos yielded no transconjugants and between donors and recipients respectively displaying TraC-Fos and TraC-Jun yielded very few transconjugants. Matings between donors and recipients lacking either TraC-LZ proteins yielded many thousands of transconjugants. Of further interest, production of TraC-Fos by recipients resulted in a strong reduction in transfer regardless of whether donors produced TraC-Fos, TraC-Jun, TraC or no TraC. These preliminary findings suggest that Fos-mediated donor-recipient cell interactions block conjugation but TraC-Fos alone in the recipient also exerts a blocking effect. The initial experiments tested for transfer of the IncF plasmid pOX38. We also tested for transfer of another F plasmid (pED208) and the IncN plasmid pKM101. In both cases, donors displaying TraC-Fos transferred the plasmids at very low frequencies to recipients displaying TraC-Fos. Thus, in contrast to our original hypothesis, we identified a potential mechanism involving the surface display of Fos LZs, or possibly the addition of purified Fos LZs, to bacteria as a means of blocking conjugative transfer. These
findings have important implications for the development of inhibitory strategies aimed at blocking the transmission of antibiotic resistance encoded by mobile genetic elements.
ABSTRACT

Apolipoprotein-E Deficiency Impairs Growth of Aortic Smooth Muscle Cell

YI GUO  Texas A&M University  Class of 2020

Sponsored by:  Yong-Jian Geng, MD, PhD, Department of Internal Medicine - Cardiology Supported by:  Texas State Higher Education Fund and Dexin-Wonder Research Grant

Key Words:  Lipoproteins, atherosclerosis, smooth muscle cell, proliferation

Background:  Apolipoprotein E (ApoE) is a lipid-transporting protein important for cholesterol metabolism. ApoE binds lipids from arterial cells and incorporate into high density lipoproteins (HDL), which deliver cholesterol to the liver to be metabolized and lowers the risk of atherosclerosis, an arterial disease causing heart attack and stroke. ApoE-deficient (ApoE/-) mice develop hypercholesterolemia and atherosclerosis. This study was designed to test the difference in growth rates between wild type smooth muscle cells (WT SMC) and ApoE/- SMC.

Materials/Methods:  WT SMC and ApoE/- SMC were isolated from aortic tissues and seeded in 12-well plates, containing 50,000 cells/mL DMEM medium/well. Cells were detached by trypsinization, and counted using a hemacytometer from day 1 to day 7 (the original seeding day being day one). Triplicate wells of cell cultures were established for each time point in all experiment groups. Each day, cells in the culture plates were observed under a phase-contrast microscope and counted. Cell growth curves were drawn by plotting the cell number/well against incubation time using the MicroSoft Excel program. The cell numbers of triplicate wells were averaged and compared statistically by Student’s t test. The data was reported as mean ± standard deviation. Probability values less than 0.05 were considered significant.

Results:  Microscopically, there was no major change observed in ApoE/- SMC compared to WT SMC throughout the study. Both ApoE/- and WT SMC showed the typical “Hill and Valley” growth pattern of SMC and they entered the exponential phase at day 2. When WT SMC cell numbers were above 40,000/well, they became less proliferative and eventually moved into the stationary phase after day 3. Interestingly, compared to WT SMC, ApoE/- SMC showed much lower numbers (< 35,000/well) at the stationary phase at day 4, indicating a significant delay (by nearly 24 hours) for the genetically defect cells entering stationary (p < 0.05).

Conclusion:  Although no major changes in morphology, ApoE/- SMC exhibit markedly lower rates of growth as compared to WT SMC. The stationary phase of ApoE/- SMC growth curve is delayed significantly, and at much lower numbers. Thus, ApoE deficiency appears to impair SMC growth.
ABSTRACT

Aortic Valve Morphology Affecting Valve Function and Aortic Diameter

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Sponsored by: Siddharth K. Prakash, MD, PhD, Medical Genetics
Supported by: Genetic Basis of Early Onset of Bicuspid Aortic Valve Disease
NIH Grant R01 HL137028-01

Key Words: BAV, Echocardiogram, Valve dysfunction, Morphology, Aortic diameter

Background: Bicuspid aortic valve disease (BAV) involves abnormalities in the aortic valve. A normal patient would have 3 cusps in the aortic valve, whereas BAV patients have 2 cusps leading to different cardiac problems, such as aortic aneurysms or valve dysfunction. BAV patients tend to have different morphologies of their valve. The orientation of the valve can vary from Type 1, Type 2, or Type 3, depending on where the raphe’s location. We decided to examine the affect of valve morphology on valve dysfunction, including aortic regurgitation and mitral regurgitation. In addition, we examined whether valve morphology expresses changes to aortic diameters. Lastly, the aortic diameter was measured over time to examine rate of increase regardless of morphology.

Methods: Following the HIPAA Release of Information protocol, BAV subjects’ physicians were contacted to get records and imaging. The RedCap online registry was used to pick 17 random echocardiograms not previously filled out. It was made sure that the 17 echocardiograms had matching echocardiographic reports. Then, using the DiCOM editing software, the echocardiograms were read to measure aortic diameters at 3 levels using the leading-edge-to-leading-edge method (Sinus of Valsalva, Sinotubular Junction, and Proximal Ascending Aorta) and determine cusp orientation. Valve function was determined from parasternal long axis view, and morphology was determined from parasternal short axis view. 258 patients were in the registry and with exclusion criteria of no echocardiogram less than a year apart with no surgery, 42 subjects were used to determine the growing ascending aorta rate.

Results: Type 1 morphology was most common with 53%, Type 2 showed 35% prevalence. 2 patients were post-op and thus did not present a specific morphology. For aortic regurgitation, the major difference occurred in the mild regurgitation diagnosis, 77.8% for Type 1 vs. 40% for Type 2 (p-value = 0.158). Type 1 had a 44.4% prevalence of no mitral regurgitation and Type 2 had 0% prevalence of no mitral regurgitation (p-value = 0.0784). P-values (>0.80) were calculated for the 3 levels of ascending aorta measurements between Type 1 and 2. The rate of the growth for the ascending aorta was 0.9438 mm/year.

Conclusion: There is no statistically significant difference between BAV valve morphology and valve function. However, our data showed aortic regurgitation and mitral regurgitation to be more prevalent in Type 2 potentially due to more floppy tissue present. No statistically significant differences were found between aortic diameters and valve morphology.
Net1A is a RhoA specific guanine nucleotide exchange factor that promotes breast cancer cell motility when it relocates from the nucleus into the cytosol. We have recently found that its relocation is regulated by the Src tyrosine kinase, an oncoprotein, which stimulates phosphorylation of Net1A on Y373, leading to Net1A relocalization into the cytosol. We have also found that the nuclear exportin CRM1 is required for cytosolic relocalization of Net1A and that phosphorylation of Net1A on S52A by JNK also promotes Net1A accumulation in the cytosol. The purpose of this project was to determine whether inhibitors of Src, JNK, or CRM1 can synergistically block Net1A cytosolic relocalization and inhibit cancer cell motility. This was accomplished by transfecting MCF7 cells with Net1A and treating them with the inhibitors at various concentrations before exposure to the stimulant EGF. We used immunofluorescence (IF) to visualize and quantify the localization of Net1A, and cell migration assays to assess cell motility. Cells were pre-treated with the JNK inhibitor at 10 µM for 30 minutes and then stimulated with EGF for 15 minutes. Net1A cytosolic localization was significantly lower in cells treated with the JNK inhibitor. For the migration assay, there were no significant differences in cell motility with the JNK inhibitor. However, there was a trend towards reduced motility in cells treated with the JNK inhibitor. Further experiments included assessment of dose dependency for inhibition of Net1A cytosolic localization by JNK and CRM1 inhibitors, and combining these two inhibitors to look for a synergistic effect. Overall, this work demonstrated that both JNK and CRM1 inhibition block Net1A cytosolic localization and laid the groundwork for testing for synergy between these inhibitors.
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ABSTRACT

Modified Hyaluronic Acid Materials for Spinal Cord Injuries

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Sponsored by: Laura Smith Callahan, PhD, Department of Neurosurgery
Supported by: Start-up funds from the Vivian L. Smith Department of Neurosurgery
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Key Words: Stem cells, spinal cord injury, blood vessels, hyaluronic acid, IKVAV

Stem cell treatments aim to restore neurological function after spinal cord injury. Preclinical models show that stem cell therapy is more effective if a tissue engineering matrix is included[1]. Di-functional hyaluronic acid (dif HA) has been shown to support neural differentiation[2], and we want to observe if including signaling peptides in dif HA (pep HA) may help blood vessel development and growth in and around the lesion area. Pep HA is made by tethering peptides Ile-Lys-Val-Ala-Val (IKVAV) to the thiol group and Leu-Arg-Glu (LRE) to the azide. These peptides have been shown to stabilize blood vessels and help them mature[3]. Four Fisher 344 rats per group were subjected to a contusion injury at the ninth thoracic vertebra and given injections two weeks later containing a 1:2 ratio of dif HA or pep HA to methacrylate HA (metHA) to form a gel. Four weeks after injection, the spinal cords were longitudinally cut using a cryostat and the sections, located 200 µm apart, were placed on specimen slides. The tissues were then stained with RECA-1 antibody, a marker for vascular endothelial tissue, which allows the blood vessels to be visualized with an inverted fluorescence microscope. The lesion areas from three sections per animal were imaged using 20x objective. Each section contained at least 80 images which were merged into large panoramas of each section using Adobe Photoshop. Using equal areas for each section, all blood vessels were counted and the diameters of at least 100 blood vessels were measured per section, starting with those closest to the lesion area. The average blood vessel diameter for pep HA injected rats (6.83 µm ± 0.74 µm, reported as average ± standard deviation) was significantly greater than that of dif HA injected rats (5.2 µm ± 0.54 µm with p=0.0217). The data indicate a trend that pep HA injected rats have greater blood vessel density (116.14 ± 14.84 blood vessels per mm²) than dif HA injected rats (102.64 ± 26.04 blood vessels per mm² with p=0.402). Di-functional hyaluronic acid with IKVAV and LRE appears to promote the maturation of blood vessels and may increase blood vessel density around the injury area.
References


ABSTRACT

Characterization of NMDA-type receptors in the Outer Plexiform Layer of Mammalian Retina

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Sponsored by: John O’Brien, Ph.D., Department of Ophthalmology
Supported by: NIH R01EY012857 to JOB
Key Words: NMDA receptors, PSD-95, Connexin 35/36, outer plexiform layer, CPP

Ionotropic NMDA receptors are a class of excitatory glutamate receptors that participate extensively in neurotransmission throughout the ganglion in brain which accept glutamate secreted from presynaptic neurons. Previously, studies have also identified non-synaptic NMDA receptors on AII amacrine cells in the inner plexiform layer of the retina that regulate the activity-driven phosphorylation of Connexin 36, a gap junction protein, and accept glutamate from spillover by neighboring synapses. The goal of this research study was to evaluate the NMDA-type receptors associated with photoreceptors in the outer plexiform layer (OPL) of mammalian retina.

To prepare the retina, a C57BL6 mouse was sacrificed at 4 PM. The retina was isolated and fixed using 2% ethylcarbodiimide hydrochloride for 30 minutes to give an eyecup which was embedded into OCT medium and later sectioned with cryostat. Immunostaining and viewing under a Zeiss LSM 780 confocal microscope were used to identify various NMDA subunits: NR1, NR2A, NR2B, NR2C, NR2D, NR3A/3B and their relative positions to PSD-95, a scaffolding protein, and to Connexin 35 (primary antibodies labelled PSD-95 proteins at the terminals of rods and cones). Results examining the OPL showed NR2A subunits both on and inside the ring-like structures of PSD-95, which the NR2A primary antibodies label the dendrite tips on the ON bipolar cells. There were no satisfactory primary antibodies that labeled NR2B, NR2C, and NR3A/3B subunits. Additionally, in the OPL, NR1 puncta were co-localized with most of the Cx35 gap junctions, while NR2A signals surrounded Cx35 gap junctions. Further studies will be to quantitatively measure co-localization and analyze retina of mice exposed to different times of the day and mice of different ages (e.g. NR2D tends to not be expressed in adult mice retina).

In a separate experiment, 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP), an antagonist selective for NMDA receptors, was used treat retina on a black mouse sacrificed at night. NMDA receptors were previously shown to upregulate phosphorylation of Cx36 gap junctions in AII amacrine cells in the inner plexiform layer (IPL) through calcium signaling. By inhibiting the NMDA receptors upstream of the calcium signaling using CPP, phosphorylation of at serine 276 and 110 of the Connexin protein in the OPL is hypothesized to decrease. The results showed that there were more Cx36 gap junctions with phosphorylated puncta in the control trial than those in the experimental trial with CPP treatment.
ABSTRACT

Searching for Upstream Regulator of the Master Virulence Control Element in *Bacillus anthracis*.

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

Supported by: The Gillson Longenbaugh Foundation and The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences.

Key Words: *B. anthracis*, AtxA, PRD, HPr

When the causative agent of anthrax, *Bacillus anthracis*, infects a mammalian host, the pathogen encounters tissue-specific signals as disease progresses. These signals include the presence of various carbohydrates. Expression of anthrax toxin has been reported to be influenced by certain sugars. AtxA, the master virulence regulator of *B. anthracis*, controls transcription of the toxin genes and other virulence factors produced by the bacterium. Thus, AtxA expression or activity may be affected by carbohydrates. The protein has multiple domains, including two bacterial phosphotransferase system regulation domains (PRD). These regions contain histidine residues that can be phosphorylated, and phosphorylation of specific histidine residues can either increase or decrease AtxA activity. The phosphotransferase system enzyme HPr, well characterized in the archetype of *Bacillus* species, *B. subtilis*, has been shown to phosphorylate histidine residues in the PRDs of transcriptional regulators. However, data from our laboratory indicates that HPr does not directly phosphorylate the PRDs of AtxA. We hypothesize that HPr has an indirect effect on AtxA by phosphorylating another PRD-containing protein that ultimately influences *atxA* expression. We found two uncharacterized genes that are predicted to encode PRD-containing proteins. To determine if these genes encode regulators of *atxA*, I developed a plan to create mutants deleted for these genes and test for effects on *atxA* expression. I cloned DNA flanking the coding sequences of these genes into a plasmid vector that facilitates creation of null-mutations in *B. anthracis*. I made the constructs in *E. coli* and subsequently transformed them into *B. anthracis*. I began culturing the *B. anthracis* transformants to allow double cross-over recombination events between the cloned flanking sequences and homologous loci. Future experiments will confirm the null-mutations and test the effect of the deletions on *atxA* transcription, toxin production, and synthesis of other AtxA-regulated virulence factors. These results will further elucidate the molecular mechanism for control of the *B. anthracis* virulence.
ABSTRACT
Calcineurin’s Role in Regulating Phosphorylation Levels of Voltage-Gated Sodium Channels in Cardiomyocytes

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Sponsored by: Shane R. Cunha, PhD, Department of Integrative Biology and Pharmacology
Supported by: American Heart Association 16GRNT30410011
Key Words: Ankyrin G, myozenin-2, calcineurin, phosphorylation, voltage-gated sodium channels

Previous research has shown that myozenin, a scaffolding protein, targets protein phosphatase calcineurin to distinct domains in cardiomyocytes—such as the transverse-tubules (Frey, N. 2000, PNAS). The Cunha lab has found a novel interaction between myozenin-2 and the membrane binding domain of ankyrin-G (AnkG MBD), an adaptor protein necessary for expression and proper targeting of sodium channels in cardiomyocytes (Mohler, P.J. 2004, PNAS; Lowe, J. 2008, JCB). The cardiac action potential is initiated by a rapid influx of sodium through voltage-gated sodium channels—mutations disrupting ankyrin-G and sodium channel association are linked to fatal cardiac arrhythmias (Mohler, P.J. 2004, PNAS). My summer research project is driven by the hypothesis that ankyrin-G organizes a macromolecular complex consisting of voltage-gated sodium channels, myozenin, and calcineurin and that calcineurin regulates sodium channel phosphorylation status, thereby influencing its activity. The project goal is to utilize biochemistry to demonstrate the interaction of the complex’s constituent proteins. To begin, I made a DNA plasmid construct of calcineurin with an HA epitope tag by PCR amplifying it from rat heart cDNA and ligating it into the mammalian expression vector pcDNA3. Protein electrophoresis and Western blot analysis allowed for visualization of the protein complexes. Thus far, we have successfully shown that myozenin-2 and calcineurin interact with the AnkG MBD. For the final experiment, the phosphorylation level of the sodium channel in protein complexes +/- calcineurin will be measured using a phospho-serine antibody. Phosphorylation of the sodium channel has different effects including altering its gating properties and increasing its expression in the cell membrane (Abriel, H. 2015, JMCC).
ABSTRACT
Electrocardiographic abnormalities in Bicuspid Aortic Valve patients

COURTNEY OLSON  Ripon College  Class of 2018

Sponsored by:  Siddharth K. Prakash, MD, PhD, Medical Genetics
Supported by:  Genetic Basis of Early Onset Bicuspid Aortic Valve Disease R01 HL137028-01
Key Words:  Bicuspid Aortic Valve, Morphology, Electrocardiograms, Valve Disease, Surgery

Background:  Bicuspid Aortic Valve (BAV) is one of the most common congenital heart diseases. It occurs when two of the cusps of the aortic valve are fused together, causing an abnormal valve shape. Many patients with this disease suffer from heart disease and aortic disease, such as proximal ascending aortic aneurysms and aortic regurgitation. Due to the abnormal anatomy of the aortic valve, there may be other conditions that are common in patients with BAV. We explored the relationship between electrocardiographic abnormalities and several disease characteristics common in BAV patients.

Methods:  Using the BAV Registry, we evaluated fifty-eight electrocardiograms (ECGs) from different subjects. We used a standardized method to score the following diseases: 1st Degree AV Block, Right Bundle Branch Block, Left Bundle Branch Block, Intraventricular Conduction Delay, and Fascicular Block. We then compared the proportions to other studies that have been read ECGs in the general, healthy population to determine the frequency of electrocardiographic abnormalities. Since prior research studies have suggested difference in disease burden between different morphologies, we used echocardiograms (echos) to determine the valve orientation. Additionally, we used the closest echo to the read ECG to determine the amount of disease in the aortic valve and the mitral valve. In the fifty-eight subjects, we collected information about whether the patients had had prior surgery on the aortic valve, aortic root or the proximal ascending aorta.

Results:  Prolongation of QRS intervals was significantly more frequent in the BAV sample when compared to two general population samples (P<0.001). When comparing Type I and Type II morphologies, ECG abnormalities were not significantly different (P>0.10). The relationship between surgical intervention and ECG abnormalities was also not significantly different (P=0.34). The abnormalities in ECGs read after surgery were not increased compared to ECGs that were read before surgery (P=0.47). The relationship between ECG abnormalities and valve regurgitation or stenosis was also not significantly different (P>0.43).

Conclusions:  In comparison to the general population, prolongation of ECG intervals was significantly more prevalent in BAV patients. There were no significant differences between patients who had pre-op vs post-op ECGs, or in subgroups with valve disease. Due to the increased prevalence of ECG abnormalities in BAV patients, further studies should explore changes in ECG abnormalities over time. Research in ECG abnormalities may lead to improved clinical care.
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ABSTRACT

Occipitocervical Dissociation: A review of Biomechanical and Treatment Considerations

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Sponsored by: Mark Prasarn, MD
Supported by: Department of Orthopaedics
Key Words: Occipitocervical, dissociation, trauma, treatment, biomechanics

Introduction: Occipitocervical dissociation (OCD) is a result of high-energy trauma causing instability at the occipitocervical junction (OCJ). The injury is associated with high levels of morbidity and mortality, but more patients with OCD have presented in the emergency department in recent years due to better spine management in the prehospital setting. Patients can have good outcomes if identified and treated appropriately. However, in many OCD cases the diagnosis and treatment can be delayed due to a lack of neurologic deficits or uncertainty regarding OCJ instability. Our goal is to apply the biomechanical data to treatment heuristics in order to identify a strategy that is accurate, feasible, and safe for deciding on operative versus non-operative care.

Methods: We searched PubMed using the terms “occipitocervical,” “craniocervical,” “atlanto-occipital,” “dissociation,” “instability,” “dislocation,” and “trauma” to identify pertinent literature for a structured review of OCD biomechanics and treatment considerations.

Results: The OCJ is held stable by a number of ligaments; only some of which are clinically-relevant for determining stability. Clinically-relevant ligaments include the tectorial membrane, capsular membrane, alar ligaments, and the cruciate ligament. Malalignment of the OCD can often be detected by using radiographic measurement systems, but some measurements may produce type II error. Two substantiated systems are available to guide operative (posterior occipitocervical fusion [OCF]) versus non-operative treatment (external orthosis) of OCD. The Harborview classification system relies on manual traction of the OCJ to determine instability and subsequent treatment. The Horn system bases treatment on MRI findings with special importance to the preservation of ligamentous structures.

Discussion: OCD has become a survivable injury if diagnosed and treated properly. We recommend that surgeons do not rely on one measurement system when diagnosing OCD, as some some lack sensitivity for non-displaced OCD. We also advocate for the use of the Horn classification system, as manual traction is contraindicated in OCD and may lead to iatrogenic neurologic injury. It seems that MRI can provide a safer and reliable alternative for identification and appropriate treatment of OCJ instability. The Horn classification system correlates well with existing data on the OCJ ligamentous complex, and has been supported by a retrospective analysis of OCD patients. In order to fully validate this system, continued multi-institutional analyses are needed to evaluate its efficacy.
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ABSTRACT

Evaluation of Light-Cured and Dual-Cured Resin Cements to Saliva Contaminated Human Enamel Using Various Dental Adhesives

ANTHONY RAFAILE The University of Texas at Austin Class of 2018

Sponsored by: Dr. Joe C. Ontiveos, DDS, MS. & Dr. Magda S. Eldiwany, DDS, MS., Department of Restorative Dentistry and Prosthodontics.

Supported by: The University of Texas School of Dentistry at Houston and McGovern Medical School Summer Research Program, Office of Educational Programs.

Key Words: Composite, Shear Bond Strength, Universal Adhesives, Resin Cements, Enamel, Dentin.

Objectives: To compare universal adhesives bonded to saliva contaminated enamel using light-cured and dual-cured resin cements.

Methods: Sound extracted human molars and premolars were first sectioned in half using the a low-speed diamond saw (Buehler Isomet). Samples were prepared using cold-cure resin liquid and powder (SampKwick) in cylinder molds then ground and polished to 180 and 320 grits silicon carbide grinding paper in a laboratory grade specimen polisher (CarbiMet 2, Ecomet 6 Polisher; Buehler). One hundred and forty-four total samples were prepared for enamel tests, n=12. Two universal, 8th generation, adhesives, [ (1) Scotchbond Universal; 3MESPE and (2) Adhese Universal VivaPen; Ivoclar] and one Total-Etch, 5th generation adhesive [OptiBond Solo Plus; Kerr ] was used in all experiments. The resin cements used included a light-cured resin cement (RelyX Veneer, A1; 3MESPE) and a dual-cured resin cement (Variolink Esthetic DC, Neutral; Ivoclar). The etching system used for the total etch of enamel was 35% phosphoric acid (UltraEtch, Ultradent). All samples were divided into two groups, one with saliva contamination and one without. Cements were bonded using a shear bond testing jig (2.2 mm d, Ultradent) and light cured using LED light at ≥500 mW/cm². Specimens were stored in 100% humidity in containers at 37°C for 24 hours. An Instron machine was used to load the specimens and calculate shear bond strength in megapascals (MPa). Data was analyzed using ANOVA and Tukey post hoc at the 0.05 level of significance.

Results: The analysis showed a significant decrease in shear bond strength values for the contamination samples compared to the non-contamination samples, p<0.001. There was a significant difference in shear bond strength among all adhesives tested, p<0.001 with Scotchbond Universal Adhesive generally showing the highest enamel bond strengths. Lastly, there was a significant difference in shear bond strength between the two cements, RelyX Veneer and Variolink Esthetic DC, p=0.014, with light-cure cement outperforming the dual-cure cement.

Conclusions: These results suggest that saliva contamination negatively effects shear bond strengths on enamel using universal adhesives. Light cured resin cement generally provides higher bond strengths on enamel compared to dual-cured resin cement.
ABSTRACT

A Double Blind Placebo-Controlled Study of CM-AT for the Treatment of Autism in Children

RAVALI REDDY  Texas A&M University-College Station  Class of 2019

Sponsored by: Deborah A. Pearson, PhD, Department of Psychiatry and Behavioral Sciences
Supported by: Grant entitled “A Phase III Randomized Double Blind Placebo Controlled Trial of LUMINENZ- AT™ (CM-AT) In Children with Autism“, sponsored by Curemark, LLC

Key Words: Autism (ASD), CM-AT, Chymotrypsin, Clinical Drug Trials

Introduction: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is estimated to affect millions worldwide. Children diagnosed with ASD have social problems, repetitive/atypical behaviors, and difficulty in verbal and nonverbal communication. Emerging research suggests that some individuals with ASD have gastrointestinal problems, including previous research done by investigators at Curemark suggesting that some children with ASD may have lower levels of a pancreatic enzyme that cleaves protein into amino acids. Amino acids are the building blocks of neurotransmitters, which are necessary for optimal brain functioning. The Blüm™ Study is a Phase III double-blind study that is examining the effect of pancreatic replacement therapy with CM-AT, to determine if it can improve functional outcomes (e.g., behavior) in children with ASD.

Methods: Children three to eight years old with ASD are eligible to be screened for this study. Children meeting inclusion criteria are randomized either to the active medication condition (CM-AT) or to a placebo condition (an inert substance identical in appearance to CMAT) for twelve-weeks. At each study visit, the child’s functional status is measured using parent questionnaires and interviews, behavioral scales, stool tests, and a physical exam. At the conclusion of the 12-week double-blind study, families are invited to have their child participate in an open-label extension of the double-blind phase project, in which all children are guaranteed to receive CM-AT.

Results: Because data collection is ongoing, no study results are yet available.

Conclusion: If CM-AT is eventually approved for pediatric use, it may help children with ASD by improving their ability to digest dietary protein and thus enhance the availability of necessary amino acids, which may ultimately improve cognitive and behavioral function in these children.
ABSTRACT

Spatiotemporal imaging of enterohemorrhagic E. coli (EHEC) gut colonization using a zebrafish model

JACQUELINE ROCHA

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Class of 2017

Sponsored by: Anne-Marie Krachler, PhD, Department of Microbiology and Molecular Genetics

Supported by: The Gillson Longenbaugh Foundation and The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences

Key Words: Gram-negative bacteria, zebrafish, food-borne infections

Enterohemorrhagic E. coli (EHEC) is a Shiga-toxin secreting bacteria whose infections cause bloody diarrhea as well as hemolytic uremic syndrome (HUS), leading to kidney failure. Infections can be acquired from contaminated food including cattle-derived products like beef and milk as cattle are reservoirs of this bacteria. Zebrafish provide an excellent model for EHEC infection due to the transparency of their larval form, which allows for the location of pathogens and the immune response to be visualized in a live host throughout the infection. Foodborne EHEC infection is induced in zebrafish larvae, where Paramecium caudatum serves as a vector carrying EHEC. Though zebrafish EHEC infections have been characterized well with regards to their transmission from infected to naïve zebrafish, the zebrafish innate immune response they elicit, and the colonization of the zebrafish gastrointestinal tract by EHEC, the fate of the vector and process of pathogen release from the P. caudatum vector have not yet been observed. My goal for this project is to characterize the ingestion of vector-borne EHEC, release from the vector and subsequent colonization of the digestive tract, using fluorescently labelled EHEC and paramecia. Together, both microbes can be tracked as they migrate through the digestive tract of the zebrafish larvae over time. A protocol has been established for the introduction of EHEC to zebrafish via paramecia, and for visualizing paramecia by staining. We show that EHEC/paramecia are found within the pharyngeal region of the zebrafish after 10 minutes of exposure to fish and reach the hindgut at around the 1-hour mark. Digestion of paramecia and EHEC release proceeds in the foregut and is completed at the 3-hour mark. Additionally, EHEC is found to spread throughout most of the gut by the second hour of feeding. These results will help guide future studies on amoebiasis, where a similar method will be employed to study the interaction and co-infection between EHEC and Entamoeba histolytica and thus aid in determining differences between symptomatic and asymptomatic E. histolytica infections.
ABSTRACT

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Sponsored by:  Nitin Tandon, M.D., Department of Neurosurgery
Supported by:  Nitin Tandon, M.D., Department of Neurosurgery
Key Words:  language, visual processing, fMRI, electrocorticography

Introduction: The two-streams hypothesis is a widely accepted model of the neural processing of vision and hearing. The hypothesis suggests that the processing of visual information is split into two distinct routes in the brain: object naming (ventral stream), and action naming (dorsal stream). After the visual information goes through the retina, it eventually reaches the calcarine cortex. It is then processed by a set of occipital regions. Visual information related to descriptive information and object identification drives ventral temporal activity, while that concerning spatial information drives parietal activity. There are 3 questions that will elucidate the roles these streams play in visual processing and language production. First, to what degree do these streams constitute independent visual, semantic, or syntactic networks? Second, what critical substrates are involved in directing the stream ventrally or dorsally? Finally, when do the twin processing streams first diverge and, later, when do these streams re-converge in a shared articulatory network?

Methods: We have had 108 patients who have been used for this experiment; 36 of them had subdural grids on the pial surface, and 72 of them had stereotactic penetrating electrodes. All of them completed the visually cued object (n=105) or action (n=85) naming tasks. On top of that, 41 patients underwent fMRI language lateralization with these tasks, affording validation of normal language activity via comparison with 19 healthy volunteers.

Results: We identified increased broadband gamma activity (BGA) during action naming in the left, language-dominant cortex localized to the intraparietal sulcus, ventral lateral prefrontal cortex, and posterior middle temporal gyrus. On the other hand, increased BGA was found in anterolateral fusiform cortex during object naming. Moreover, we found 9 distinct nodes shared between the tasks for articulatory support: pre-SMA, SMA-proper, anterior insula, pars triangularis, pars opercularis, anterior and posterior subcentral gyrus, the Sylvian parietal-temporal junction, and superior temporal gyrus. We observed increased BGA in this bilateral articulatory network during verb production compared to noun production, most likely because of the increased lexical and syntactic demands associated with verb production.
Conclusions: These experiments are helpful in characterizing the temporal dynamics and magnitude of cortical activity that subserves cognitive processes involved in action and object naming. Increased understanding of the language production networks in the brain will help further the development of improved treatment for people with damaged language faculties.
ABSTRACT

Endothelial Pak1 Upregulation Reduces Neuronal Cell Death In Vitro

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Sponsored by: Louise McCullough M.D., Ph.D, Neurology Department
Supported by: Louise McCullough M.D., Ph.D
Key Words: Pak1, stroke, mice, neuroprotection

Background: Ischemic stroke occurs when blood flow to the brain or regions of brain is stopped or reduced leading to brain injury and neurological deficits. Stroke affects primarily the elderly population, and it is the fifth leading cause of death and the leading cause of long term disability in the US. However, t-PA is the only approved pharmacological treatment for this disease and has a very narrow therapeutic window owing to its potential effects to cause cerebral hemorrhage. p21-activated kinase 1 (Pak1) has been shown to regulate angiogenesis, apoptosis, and has been implicated in many neurological disorders. Although its role in stroke is not clear, it has been shown to regulate BDNF, a potent neuroprotective factor primarily secreted by endothelial cells. Therefore, we tested the hypothesis that endothelial Pak1 is neuroprotective and the potential protection is mediated by BDNF after stroke.

Methods: Primary mouse neuronal and cerebral endothelial cells were cultured. A range of doses of lentivirus encoding Pak1 were applied to the endothelial cells. Neuronal and endothelial cell cultures were placed in oxygen-glucose deprivation (OGD) conditions for 1.5 and 16 hours, respectively. Following re-oxygenation (24 and 48 hours, respectively), BDNF concentration in endothelial cell culture media was measured using an enzyme-linked immunosorbent assay. The media was then transferred to the neuronal cell culture. Neuronal cell death was measured using a cell count kit, 24 hours after media transfer.

Results: In the endothelial cell cultures that received the OGD treatment, there was a significant, dose-dependent response in BDNF levels as the Pak1-lentivirus treatment increased. This corresponded to reduced neuronal death in a similar dose-dependent manner, when neurons were treated with endothelial media following OGD. In the endothelial and neuronal cell cultures that did not receive the OGD treatment, there was no significant change in endothelial BDNF or neuronal death.

Conclusions: Endothelial Pak1 upregulation was shown to increase BDNF levels in a dose-dependent manner. Consequently, neuronal death following OGD treatment was reduced using cell media from endothelial cells with Pak1 overexpression. This confirms our original hypothesis that overexpression of endothelial Pak1 upregulates BDNF expression, which would protect neurons during stroke. In future studies, we will move our findings to an in vivo stroke model. We will manipulate Pak1 in endothelial cells in mouse brain using vectors that have endothelial specific promoter and observe its impact on stroke outcome including both brain infarcts and mouse behavior.
ABSTRACT

Apn2 Catalysis is Necessary for Increased Mutation in Apn1 Knockouts

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Sponsored by: Nayun Kim, PhD, Department of Microbiology and Molecular Genetics

Supported by: The Gillson Longenbaugh Foundation, The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, GSEC SURP

Key Words: Base excision repair, Apn1/Apn2, transcription associated mutagenesis

Base excision repair (BER) is an important DNA repair pathway that excises and replaces a single damaged nitrogenous base. As with any DNA repair mechanism, a thorough understanding of this pathway is valuable for elucidating how cancer may develop. DNA glycosylases first excise the base, leaving a highly mutagenic abasic site. This abasic site is then acted on by AP Endonucleases. In *Saccharomyces cerevisiae*, the major and minor AP Endonucleases are Apn1 and Apn2, respectively. It has previously been shown that when Apn1 is disrupted, the persisting abasic sites result in transcription associated mutagenesis (TAM). Interestingly, when Apn1 is knocked out, the mutation rate increases by 100-fold in YEPGE (glycerol ethanol) media, but only 3-fold in YPD (dextrose) media. Additionally, deletion of Rfx1 (repressor of Apn2) in an Apn1 knockout increases mutation rate by 10-fold in YPD. However, in *apn1 apn2* double knockout, the mutation rate is low and there is no significant difference between the rates in the two media. Therefore, it is hypothesized that Apn2 increases mutation rate in the absence of Apn1. The goal of my project is to determine whether this increase in YEPGE compared to YPD is caused by a higher rate of transcription or a higher catalytic activity of Apn2. To accomplish this, *apn1 apn2* double knockouts were transformed with two different plasmids: 1) containing Apn2 under the control of constitutively active pGPD promoter and 2) containing Apn2 gene with a mutation that renders it catalytically inactive, also under the control of the pGPD promoter. The mutation rates were then calculated for each new type of yeast strain using a reversion reporter assay. Compared to the empty control vector, there was no significant difference in the mutation rates for the strain with catalytically inactive Apn2. However, there was a 3-fold increase in the mutation rate of constitutively active Apn2 in YEPGE, although there was no increase in YPD. Therefore, we conclude that catalytic activity of Apn2 is necessary to increase mutation rate. Since we see vastly different results in the two systems that should contain constitutively expressed Apn2, further testing needs to be done to further understand how the transcription rate of Apn2 affects mutation rate. The next step is to perform an RNA extraction on the *apn1 rfx1* double knockout and compare Apn2 expression levels to the Wild Type and the *apn1* knockout to determine whether the Apn2 is in fact constitutively expressed.
ABSTRACT

Bone marrow stromal cells promote increased prostate cancer cell proliferation and cluster size in a novel 3D cell culture system

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Rice University

Background: Prostate cancer (PCa) is a slowly progressing disease, but upon metastasis, primarily to bone, the five-year survival rate decreases significantly from 99% to 29%. In wounded tissue, stromal cells promote wound healing responses by increasing the production of extracellular matrix (ECM) components, growth factors, and more. However, in most carcinomas, this same mechanism supports cancer growth and metastasis. It is known that the interactions between PCa and bone marrow stromal (BMS) cells in the bone-metastatic tumor microenvironment (TME) promote the growth of PCa. Therefore, in this study, I sought to culture PCa and BMS cells in a biologically relevant model by using a three-dimensional (3D) hydrogel system, designed to mimic the bone microenvironment, to reproduce the interactions between PCa and the stroma that occur in vivo.

Methods: BMS cell line, HS-27a, and PCa cell line, C4-2B, were cultured in complete RPMI under standard cell culture conditions. At confluency, cells were trypsinized and encapsulated in a 3D system composed of collagen I/Hyaluronic Acid (HA) under three conditions: HS-27a alone, C4-2B alone, and coculture of both cell types. Cell viability was tested on days 2, 7, and 12 using a live/dead assay. On day 9, one set of gels was stained for CK-18, an epithelial cell marker, and Ki-67, a proliferation marker. Another set was stained for CK-18 and vimentin, a stromal cell marker. On day 12, C4-2B cluster size was measured using CellProfiler™. C4-2B cells were quantified using CellProfiler™ and Imaris®.

Results: Cell viability was greater than 95% on days 2, 7, and 12. C4-2B cluster size on day 12 was significantly larger in the coculture than in the monoculture (p=0.0273). Additionally, there was a significantly greater number of C4-2B cells on day 9 in the coculture than in the monoculture (p=0.0002). CK-18 and vimentin staining displayed minimal physical interaction between the C4-2B and HS-27a cells.

Conclusions: The significantly larger C4-2B cluster size and greater number of C4-2B cells in the coculture versus the monoculture indicates that the HS-27a stromal cells support C4-2B tumor growth and proliferation in 3D culture. The minimal physical interaction between the C4-2B and HS-27a cells suggests that the cells communicate primarily through paracrine signaling.
ABSTRACT

Phenotypic characterization of the ACTA2 R149C mutation in smooth muscle cells

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Sponsored by:  Dianna M. Milewicz, MD, PhD, Department of Medical Genetics
Supported by:  John Ritter Research Program
Key Words:  Aneurysm, contractility, proliferation, α-actin, SMC

BACKGROUND: Thoracic aortic aneurysms and dissections (TAAD) kill about 15,000 Americans each year. 20% of patients with TAAD have a genetic predisposition inherited in an autosomal dominant pattern. Underlying mutations cause aortic abnormalities that can lead to weakening of the aortic wall (dilatation), bulging out of the aortic wall (aneurysm), or tearing of the layers making up the aortic wall (dissection). The most common mutations leading to TAAD are heterozygous missense mutations in the gene encoding smooth muscle α-actin, ACTA2. A subset of ACTA2 mutations have been shown to lead to vascular occlusive diseases as well as TAAD. The R149C mutation is the most common ACTA2 mutation and can lead to premature onset of coronary artery disease, TAAD, and even stroke.

METHODS AND RESULTS: To study the R149C mutation further, human SMCs harboring the mutation and genetically engineered mouse aortic tissue samples were phenotypically characterized in vivo and in vitro using cell proliferation analyses, quantification of contractile and inflammatory gene expression, and immunofluorescence of actin filaments in the context of TGF-β signaling. R149C mutant human SMCs were found to have increased proliferation, but no change in the expression of contractile proteins or the localization of myocardin related transcription factor-A (MRTF-A) compared to controls. However, R149C mutant mouse tissue samples were found to have increased expression of both contractile genes and several inflammatory markers. The aortas were also sent for contractility analysis and were found to have decreased contractility.

CONCLUSIONS: These data may indicate that the mutant SMCs, when isolated, express a mild phenotype, but in the aorta, where they are subject to hemodynamic forces, overcompensate for their decreased contractility by overexpressing contractile genes and elaborating compounds associated with the initiation of local inflammation.
ABSTRACT

The Function of *S. cerevisiae* and *L. kluyveri* Ski7 in Nonstop mRNA Decay

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Sponsored by: Ambro van Hoof, Ph.D., Microbiology and Infectious Diseases

Supported by: Gillson Longenbaugh Foundation, NIH/NIGMS

Key Words: mRNA decay, nonstop decay, gene duplication, Ski7p

The purpose of this project is to further characterize how the *Saccharomyces cerevisiae* protein Ski7 has changed over evolutionary time. The *S. cerevisiae* SKI7 gene and its paralog HBS1 evolved from a single alternatively spliced gene called SKI7/HBS1. After a whole genome duplication event about 100mya, the copies of this ancestral gene stopped being alternatively spliced and eventually each encoded one protein, Ski7p or Hbs1p, with a distinct role in mRNA decay. Ski7p is known to function in general mRNA turnover, but also has a specific role in the decay of transcripts lacking an in-frame termination codon (nonstop mRNA decay). It was previously unknown whether the ancestral, alternatively spliced SKI7/HBS1 encoded a version of Ski7p that functioned similarly in nonstop decay. To investigate this, a proxy of the ancestral version of the gene (sourced from the closest preduplication relative of *S. cerevisiae*, *Lachancea kluyveri*) was expressed in *S. cerevisiae*. Previously, it was shown that Ski7p from *L. kluyveri* (LkSki7p) was nearly as effective as Ski7p in preventing expression of his3-nonstop enzyme activity, but not very effective in preventing accumulation of pgk1-nonstop mRNA. I tested the hypothesis that LkSki7p is effective in preventing protein accumulation, but not in preventing mRNA accumulation by comparing the effects on both protein and RNA levels for two reporter genes. My results indicate that LkSki7 is not effective in preventing either protein or mRNA accumulation, suggesting the hypothesis is false. Future investigations will determine if the reason for this deficit in function is due to changes in the structure of LkSki7p that have occurred since that lineage’s divergence or if it is due to ScSki7p having specialized in its nonstop decay function.
ABSTRACT
Evaluating Machine Learning MRI Assessment Protocols

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Sponsored by: Refaat E. Gabr, PhD, Department of Diagnostic and Interventional Imaging
Key Words: Quality Control, Cross-validation

Poor image quality is an ongoing issue for many researchers working with magnetic resonance imaging (MRI). Traditionally, experts visually inspect each image prior to use in clinical and research settings. This can be a time consuming task due to the large number of scans in today’s imaging centers. Image quality assessment is also prone to high variability due to undetected artifacts and inter- and intra-rater variability. Additionally, a progression towards collecting large samples from multiple sites with site and acquisition protocol differences possibly increases the variability within the data set. More recently, researchers have been attempting to develop automated quality control protocols to standardize the quality of images used in future research and clinical testing. Automated quality control protocols will save time and reduce bias and variability in quality assessment.

Gradient boosting is a machine learning method that is robust to heterogeneous data and detects non-linear feature interactions. We therefore propose that a gradient boosting classifier (GBC) has the potential to be more sensitive and specific at identifying poor quality MRI images when compared to other popular methods such as support vector machines classifiers (SVC) and random forest classifiers (RFC). We used the Autism Brain Imaging Data Exchange (ABIDE) dataset (N=1102) and the UCLA Consortium for Neuropsychiatric Phenomics LA5c Study (ds030) dataset (N=266) for classifier development because of their heterogeneity and pre-rated images. Processing each anatomical image through an automated feature extraction program (MRIQC) yielded 14 image quality metrics spawning 56 features. The features were used for classifier training. The following procedure was performed with and without z-score transformation on the features for a linear SVC, radial basis function (rbf) SVC, RFC, and GBC. A nested cross-validation of the ABIDE dataset was performed to select hyperparameters for each classifier optimizing the area under the curve (AUC) of the receiver operating characteristics curve, classifier accuracy, sensitivity, and specificity respectively within the inner cross-validation and evaluating performance in the outer cross-validation. We then used a single cross-validation of the ABIDE dataset with a refined search of the classifier hyperparameters to better optimize the performance. Each cross-validation was repeated 100 times to ensure model validity. Finally, we evaluated the performance of the classifiers on the ds030 dataset.

We report the best AUC at 0.80 ± 0.12 with RFC classifier, best accuracy 0.89 ± 0.07 with RFC classifier, best sensitivity at 0.82 ± 0.27 with GBC classifier, and best specificity at 1.00 ± 0.00 with rbf SVC, RFC, & GBC classifier. These results indicate that a GBC or a RFC are able to assess image quality with acceptable accuracy, and could therefore be included in automated and real-time quality procedures.
ABSTRACT

Effects of COMP on Ligament Fibril Organization

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Sponsored by: Karen Posey, PhD, Jacqueline Hecht, PhD, Pediatric Research Center
Supported by: NIH grant (#1R01AR057117), Leah Lewis Family Foundation
Key Words: Pseudoachondroplasia, ligament, collagen type 1

Background: Pseudoachondroplasia (PSACH) is a short limb dwarfism associated with severe joint pain starting in childhood and early onset osteoarthritis related to joint erosion. Physical characteristics include shortened long bones, windward/bowed/knocked knees, and lax joints. Laxity can cause joint misalignment, which causes joint injury due to improper distribution of mechanical stress from physical activity. In this project, we focus on ligaments, the collagenous fibrillar tissue connecting bones, to better understand joint laxity.

Mutations in thrombospondin 5 (TSP-5), commonly referred as cartilage oligomeric matrix protein (COMP) cause PSACH. Mutations in COMP leads to protein retention in the endoplasmic reticulum and ultimately premature chondrocyte death leading to short stature. COMP is an extracellular matrix protein abundant in ligaments, tendons, and cartilage. COMP interacts with matrilin 3 and collagen type IX, participates in chondrocyte proliferation, and regulates fibril diameters in collagen type I and type II. The majority of ligament tissue is composed of type I collagen fibrils. The goal of my project is to understand the effect of mutant COMP on ligament microarchitecture by evaluating the distribution of type 1 collagen fibrils, which regulate joint laxity.

Methods: Patellar ligaments from C57BL/6J (C57), COMP null (COMP-/-), mutant-COMP-Col II (MT-COMP-II) and mutant-COMP-COMP (MT-COMP-C) mice were collected and processed for electron microscopy. The MT-COMP-II and MT-COMP-C mice both express D469del human mutant COMP but expression is driven by mouse type II collagen II promoter or the human COMP promoter respectively. We measured collagen fibril diameter from EM images of ligament cross sections using Bioquant software. The distribution of type I collagen fibril diameters were compared among the different genotypes.

Results and Conclusion: The greatest percentage 20.13% of C57 control samples, fibril diameters fell within the range of 120 to 140 nm, with 23.27% of fibrils greater than 140 nm and the remaining 56.6% were thinner than 120 nm. Mutant COMP increased the percentage of fibrils greater than 160 nm as shown by the comparison of the MT-COMP-II and MT-COMP-C with control C57. The complete absence of COMP (COMP-/-) caused the fibril distribution to change to bimodal with the first peak at 40-60 nm and the second peak 120-140 nm and there was a significant percentage of large fibrils greater than 140nm compared to control (C57).
ABSTRACT

Bacteriophage T7 DNA translocation during infection is bolstered by the host ATP synthase complex

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Class of 2020

Sponsored by: Jun Liu, PhD, Department of Pathology and Laboratory Medicine
Supported by: Jun Liu, PhD, Department of Pathology and Laboratory Medicine, The University of Texas at Houston Medical School – Office of the Dean
Key Words: Bacteriophage T7, cryo-EM, ATPase, translocation, infection

Background: Phage Therapy has become an increasingly popular method to treat pathogenic bacterial infections as it utilizes specific lytic bacteriophages to target bacteria with little risk of killing essential bacteria. Therefore, it is pertinent to understand the infection process and mechanisms of bacteriophages. T7 is a bacteriophage that infects Escherichia coli through forming an infection complex utilizing viral proteins gp 14, gp 15, and gp 16 to form an intermembrane channel in order to translocate its DNA. To visualize the infection complex and process, we used cryo-electron microscopy (cryo-EM) to study the relationship of the bacterium and virus.

Methods: Tilt-series of vitrified Wild-type T7 bacteriophage infecting E. coli minicells were collected in a FEI TF30 Polara operating at 300 KeV and imaged using a Gatan K2 Summit Direct Electron Detector operating in counting mode taken at a nominal magnification of 15,500x which corresponds to a sampling of 2.5Å/pix. This data was then aligned using IMOD and tomograms were reconstructed with Tomo3d. Subtomograms were then averaged. Final global averages were visualized using UCSF Chimera and the atomic structure of F1-ATPase from E. coli was docked into the discovered unknown cytoplasmic density using rigid body fitting.

Results: A transmembrane channel formed after adsorption of T7 on the cell wall of the bacteria and an unknown cytoplasmic density subsequently appeared in wild type (WT) E. coli and rough Salmonella enterica. The complex was also not observed in ATP synthase deficient E. coli mutants and lipopolysaccharide (LPS) vesicles. After ejection of the viral genome into the host cell, both the transmembrane channel and cytoplasmic complex disappeared.

Discussion/Conclusion: There is strong evidence to support that the cytoplasmic density discovered may be the host cell’s ATPase. In both WT E. coli and rough S. enterica which are capable of producing ATPase, the cytoplasmic densities appear when infected by T7 whereas LPS vesicles and ATPase-deficient E. coli which are unable to produce ATPase did not display the densities when infected by T7. T7 is capable of growing on WT E. coli and rough S. enterica, suggesting that the complex is not host-specific. The complex was not observed in ATP synthase deficient E. coli mutants, suggesting that the complex functions in an energy
dependent manner. We hypothesize that if the structure is F1-ATPase, it would aid in the genome translocation for the T7 bacteriophage after recruitment to the complex, thus making it more “fit” than virions that cannot recruit the host cell’s ATPase for the same purpose since T7 is capable of infecting its host cell without the assistance of ATPase.
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International Students
International Medical Students
ABSTRACT

Targeting Bruton’s Tyrosine Kinase with X-aptamers

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Sponsored by:  David E. Volk, Ph.D.

Keywords:  X-Aptamers; Bruton’s tyrosine kinase; influenza

Respiratory ailments account for 25 to 30 percent of both outpatient visits and hospitalizations among US military personnel. Specifically, influenza results in hundreds of hospital stays every year. Although the military population is highly immunized against influenza (>90%), it is not unusual for outbreaks to occur. Mounting evidence supports that PMNs contribute to excessive acute inflammatory responses and may function as direct triggers of the lung pathophysiology observed in many patients with influenza. Work by the Kurdowska group at UTH Northeast has revealed an essential role of Btk (Bruton’s tyrosine kinase) in controlling pro-inflammatory functions of PMNs in lungs. In particular Btk causes autophagy both in vitro and in vivo. We hypothesize that X-aptamers, small oligonucleotides with selected protein-like side chains, can be used to modulate the function of Btk and diminish the pathology of influenza infections. In addition, they can be ligated to a variety of siRNA molecules for dual effect therapy.

Using methods previously described (Lokesh et al., Methods in Mol. Biol. 2017), we developed and tested putative X-aptamers targeting Bruton’s tyrosine kinase (Btk). The lead XA, called BTK4772 (confidential sequence), and others, were synthesized on an Expedite 8909 oligo synthesizer, and purified by reverse phase chromatography on an Akta 10 purifier using a Hamilton PRP-1 semi-prep column. The results of an earlier small animal trial were promising, and thus a second large-scale animal test is needed to confirm these results. This summer, we synthesized and purified a large scale batch of BTK4772 for this upcoming animal study. The results of this study will not be known for several months.
ABSTRACT

Studying Translational Fidelity in Bacteria

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Sponsored by: Jiqiang Ling, Ph.D, Department of Microbiology and Molecular Genetics
Key Words: Protein synthesis, fidelity, single cell

Bacterial infection still makes a great percentage of infection in clinical practice despite the progress in antibiotics. Since the infection can be life-threatening, especially in surgeries, the necessity for the study of bacterial growth pattern and how the bacteria deal with challenges becomes obvious. Faithful translation is an essential part of gene expression, which is the basis of the growth of bacteria. Loss of fidelity during translation is therefore generally considered harmful to the bacterial growth. In the previous studies, our lab has demonstrated that, surprisingly, moderate increases in ribosomal error rate, has provided Escherichia coli, a G- (Gram stain negative) bacteria, with a greater tolerance to oxidative stress. Additionally, our lab has found that the ribosomal error rate between single cells in a wild type E. coli population is highly heterogeneous. This is accomplished with a dual fluorescence reporter system— mCherry-YFP (m-y, red and yellow fluorescent proteins) fusion reporters that measure the errors of stop-codon readthrough (UGA) and frameshifting. Since our focus was mainly on the G- bacteria, we wonder if the G+ bacteria will present such phenomenon as well. Hence, the overall goal of my project is to transform the plasmid with the reporters to measure translation fidelity noise quantitatively into Bacillus, a G+ bacteria.

To achieve this goal, I used E. coli plasmid with reporters initially. I did PCR (polymerase chain reaction) on the reporters for elongation, and then restriction to digest the reporters and Bacillus plasmid to make them have the same ends that can be ligated together. After the digestion, I ligated the reporters to the Bacillus plasmid and did transformation. When all the steps were done, I did PCR and sequencing to validate the newly constructed plasmid. I got bacteria growing on the plates after transformation, however, during validation, the results turned out to be negative. I repeated the experiments twice, but none of them were positive. This was likely because that the two restriction points were too close to each other. Owing to the limited time, the goal was not achieved completely.

We might get Bacillus plasmid with reporters and prove that G+ bacteria with moderate ribosomal error rate will also present resistance to oxidative stress. Nevertheless, due to the time issue, a definitive conclusion cannot be reached and requires further studies.
ABSTRACT

Echocardiography in Mice with Atherosclerosis: A Non-Invasive Assessment of Cardiovascular Structures and Function

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Sponsored by: Yong-Jian Geng, MD, PhD, Department of Internal Medicine-Cardiology
Supported by: University of Texas Houston Medical School Summer Research Program
Key Words: Lipoprotein, atherosclerosis, hypercholesterolemia, echocardiography

Background: Apolipoprotein E (ApoE), an apolipoprotein synthesized primarily by the liver, constitutes a key protein component in several lipoprotein particles essential for cholesterol metabolism. The deficiency of Apo E impairs the clearance of cholesterol from peripheral tissues, resulting in the development of hypercholesterolemia and atherosclerosis. Mice genetically lacking ApoE develop hypercholesterolemia and atherosclerosis, mimicking human diseases.

Hypothesis and Aim: This study aimed at testing the hypothesis that Apo E knock-out (ApoE-/-) mice are prone to atherosclerosis with narrowing arteries and malfunctional hearts, which generate a phenotype suitable for non-invasive assessment by ultrasound imaging of anti-atherogenic effects of therapeutic agents. The long-term goal was to determine whether the deficiency of ApoE alters cardiovascular function and thus increases the risks of atherosclerosis.

Methods: ApoE-/- mice and their wild type (WT) counterpart C57BL/6J mice (6 months old, male and female mixed together, WT n=27, ApoE-/- n=21) were examined by echocardiography (Visualsonics Vevo 770™ Imaging System). Under anesthesia, the body weights of mice were measured and echocardiography was performed. The parameters of cardiovascular morphology and function included the left ventricular stroke volume (SV), ejection fraction (EF), fraction shortening (FS), and cardiac output (CO) as well as intima-media thickness of the aorta. Then, all the measurements underwent statistical analysis. When p<0.05, the difference in the parameters between the two groups of mice were considered significant.

Results: While the body weight of ApoE-/- mice appeared lower than WT mice, the intima-media thickness of their aortas showed a marked increase (p<0.05). The cardiac function of ApoE-/- mice had a tendency of deterioration, and yet statistically no major difference was detected between WT and ApoE-/- mice, perhaps due to limited numbers of the mice and their relatively younger ages.

Conclusions: Non-invasive measurement with ultrasound imaging is a useful method to assess early atherosclerosis developed in the aortic intima of ApoE-/- mice, prior to the development of cardiac dysfunction.
ABSTRACT
Neuroprotective effects of ETAS in APP overexpressed mice

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Sponsored by: Anil D. Kulkarni M.Sc, PhD, Department of Surgery
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Key Words: ETAS, neurodegeneration, Alzheimer's disease, HSP,

Background/Aims: The human body exhibits various stress responses via the autonomic nervous, endocrine, and immune systems, which are mediated by the hypothalamus and interact with complicated biological defense reactions. Enzyme-treated asparagus extract (ETAS), has been developed as a functional compound produced from the asparagus stem. Investigators have shown that ETAS showed neuroprotective effects and attenuates cognitive impairment in senescence-accelerated mice (Sakurai and others 2014). Furthermore, Ito et al. (2014) have reported that ETAS might exert anti-stress effects under stress conditions, via enhancement of Heat Shock Protein. Also the ability of chaperones such as HSP to protect against neurodegeneration is consistent with the view that soluble misfolded proteins are neurotoxic (reviewed by Muchowski, 2002; Auluck et al., 2002). The overall goal of this research project is to determine whether ETAS restore memory function through overproduction of HSPs-induced decrease apoptosis in senescence-accelerated mice.

Hypothesis: We hypothesize that ETAS restore memory function through overproduction of HSPs-induced decrease apoptosis in APP-overexpressed mice. (Alzheimer's disease model)

Experimental Design/Results: Neuroprotective effects of ETAS in 6-8 weeks old; 20-24 grams APP overexpressed mice (a double transgenic - APP and PS1) mouse strains with 129s6 background) were successfully generated in our laboratory. Animals were divided into 5 groups. Group 1: APP mice were pre-treated with saline. Group 2: APP mice were pre-treated with ETAS at a dose of 200 mg/kg, Group 3: APP mice were pre-treated with ETAS at a dose of 1000 mg/kg. Group 4: wild type mice were pre-treated with saline. Group 5: WT mice were pretreated with ETAS at a dose of 1000 mg/kg. ETAS was administered by gavage daily for 1 month. Saline, the vehicle for ETAS was administered daily by gavage for one month. The Morris Water Maze (MWM) was used to assess the cognitive function of mice. After the MWM completed, animals were sacrificed and their brains were removed for further assays.

Results: Morris water maze test showed significant prolongation of time spent in the target quadrant in both Group 2 and Group 3 animals. (p<0.05, p<0.01 respectively) Additionally, immunofluorescence staining in cryosectioned mouse hippocampus tissues measured by relative fluorescence unit (RFU) validated the increase production of HSP27 in both Group 2 and Group 3 compare to Group 1 APP mice (p<0.01, p<0.01) On
contrary, we validated the decrease production of βamyloid protein between Group 1 and Group3 (p<0.05)

Discussion: Our data suggest that ETAS can restore memory function through overproduction of HSPs. Further studies are needed to confirm the HSP70 induced apoptosis in APP mice. We used APP transgenic mice model to study stress induced inflammation could contribute the neurodegeneration.
ABSTRACT

Lactoferrin Immune Modulation of Macrophage Activation
Via Toll-Like Receptor pathways

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Sponsored by: Jeffrey K. Actor, Ph.D. and Shen-An Hwang, Ph.D., Department of Pathology and Laboratory Medicine, UTHealth McGovern Medical School

Keywords: Immunology, Lactoferrin, Macrophage, Toll-Like Receptor, TLR, Cytokines

Lactoferrin is an iron-binding glycoprotein that is an integral component of the innate immune system. It is found in many body fluids and secretions, and concentrated at mucosal surfaces. Lactoferrin exhibits diverse biological activities ranging from activation of innate immunity to direct microbicidal and anti-cancer cell effects. It possesses several immune modulating properties, including pleiotropic effects on macrophage activity and function. However, the pathways for lactoferrin mediated macrophage activation events in innate immunity are not entirely clear. These studies were designed to clarifying the mechanism for lactoferrin activation of macrophages, and integral component cell of the innate immune response.

Toll-like receptor (TLR) pathways are major regulators of the innate immune response. The macrophage cell line J774A.1 was utilized as a model to examine activation with TLR agonists, in the presence or absence of Lactoferrin. Cells were cultured with agonists, and proinflammatory mediators were assessed after 48 hours incubation, by enzyme linked immunoadsorbant assay (ELISA). Stimulators used were heat killed Listeria monocytogenes (HKLM; TLR2 agonist), lipopolysaccharide (LPS; TLR4 agonist), Lactoferrin (putative activator via CD14 and/or TLR-4), or heat killed Bacillus Calmette-Guérin (BCG). Responses elicited were compared to cells lines deficient in surface receptors TLR2, TLR4, TLR2/4, CD14, or cells missing intracellular TLR activating component MyD88.

Lactoferrin added to HKLM or to LPS treated J774A.1 cells demonstrated decreased production of TNF-α and IL-6. Likewise, TLR4KO and CD14KO cells also demonstrated decreased cytokines in the presence of Lactoferrin. However, assessment on the TLR2KO cells did not reveal changes cytokine production due to Lactoferrin incubation with agonists. This result suggests that Lactoferrin may interact with the TLR2 pathway, a previously unidentified pathway. Furthermore, these experiments call into question the validity of the published work identifying CD14 and TLR4 as receptors for Lactoferrin-induced cell signaling. Further work is warranted to fully assess the Lactoferrin receptors and associated mediated events.
2-months Clinical Observership at Memorial Hermann Hospital,
University of Texas Health Science Center at Houston

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Sponsored by: Dr. Sunil Sheth
Supported by: Department of Neurology - McGovern Medical School
Key Words: Clinical, Stroke team, ED, Gratitude

The first day I met my mentor Dr. Sunil Sheth I told him about my goals and expectations this summer which is to learn more about what the clinical field is like here in the US and to have more opportunity to see the patient-docter interactions here. Dr. Sheth understood me very well and sent me to go with the stroke team, which enables me to be a part of the health care system of the United States and ended up being a great learning experience in my life as a med student.

I spent the first three weeks going with the stoke team which is composed of one attending physician, a stroke fellow, a senior resident and several interns and medical students. Usually the rounding starts at about 8:30 in the NICU. The first thing we do in the team is to let the attending know the patients’ medical condition overnight and go over the new imaging results of those patients. And then the team goes into the ICU ward to check the patients and talk to their family about the next plan for the patient. Then we go to to the stroke unit and basically do the same thing as in NICU. There are also many useful lectures for residents and medical students. I went to several of those: a review of cranial nerve function and related diseases by Dr. Martin, one about dyskinesia by Dr. Mya Schiess and one about hypodensity and hyperdensity on CT scan by a physician from radiology, which I found very interesting and meaningful.

For the following three weeks, I went down to the ED to shadow one of the their ER senior residents there and sometimes go with Jazba to see some stroke codes. Usually the ER residents get pretty busy that they barely have time to teach me something but I think I still learn some thing in there. The other day I assisted an resident doing a central line to a older male patient. It is a totally sterile procedure in which the resident first used the ultrasound to locate the patient’s femoral vein and then stick in a big needle and put in a wire through the bore of the needle and pull out the needle, then using another device to dilate the patient’s vein and finally put in a catheter all the way up to the IVC. And I also happened to see ER docs performing valsalva procedure for a female patient with supraventricular tachycardia and draining blood from the penis of a patient with priapism.

In summary, I really spent a great summer here in TMC and I really want to express my gratitude to Dr. Sheth for letting me have this opportunity here and Alicia and Jazba for being like an umbrella covering me and showing great patience to me these days. I will miss you guys.
ABSTRACT

A Video Says A Thousand Words: A Pilot Program of Video-Based Education in Surgical Training

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Class of 2019

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Supported by: LBJ Hospital Department of Surgery
Key Words: Video-based education, Laparoscopic cholecystectomy

Introduction

Video-based education is an important training tool for individuals to learn and improve, particularly in highly technical activities such as sports or surgery. Watching demonstrations of good and poor technique, as well as self-review, may dramatically influence an individual’s understanding of the procedure. The aim of this project was to develop a pilot program of video-based education for surgical residents and implement a process of self-education.

Methods

This was a single-center, quality improvement project at the Lyndon Baines Johnson General Hospital department of General Surgery. Following informed consent, videos of 20 laparoscopic cholecystectomies were obtained. Utilizing Adobe Premiere Pro CC 2017, all videos were edited to 10-minute montages. Three senior surgeons viewed the videos and graded each one as “easy” or “difficult” cholecystectomy and then assigned a grade of “good”, “average”, or “poor” surgical technique.

Results

Videos of “good” or “poor” surgical technique were reviewed (video 1 and video 2 as example). All surgical residents observed the edited videos and discussed the technique.

Conclusions

Video-based education is a crucial aspect for medical training, particularly technically based specialties such as surgery. Future studies are needed to assess the impact of video-based training for novice surgeons and experienced surgeons learning new procedures, as well as the impact on clinical outcomes for patients.

video 1(good): https://youtu.be/BvMQXQKZnjY
video 2(average): https://youtu.be/NhWyNBYG-qY
ABSTRACT

Identification of Homozygous Mutations in Thoracic Aortic Aneurysms and Dissections (TAAD)

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Key Words: Mutation, Thoracic aortic aneurysms and dissections, Whole exome sequencing

Background: The major diseases affecting the thoracic aorta are thoracic aortic aneurysms and dissections (TAAD). Approximately 20% of patients with TAAD have a family history of TAAD but do not have evidence of a genetic syndrome, referred to as familial TAAD (FTAAD). Analysis of FTAAD pedigrees indicated that the inheritance pattern of TAAD in the majority of these families is autosomal dominant and causative mutations in a number of genes for FTAAD are heterozygous mutations. Interestingly, a homozygous and a compound heterozygous mutations in LTPB3 were recently identified in two families with FTAAD, suggesting that autosomal recessive inheritance may also be pathogenic in TAAD.

Methods: Our laboratory performed whole exome sequencing (WES) on 366 individuals with early age-onset (< 56 years old) of sporadic thoracic aortic dissection (ESTAD). Analysis of the WES found that 9.3% of these patients have heterozygous mutations in known FTAAD genes. To identify novel genes with putative homozygous mutations for TAAD, we reanalyzed ESTAD WES data for rare, homozygous variants that have minor allele frequencies less than 0.005 in European American or African American cohorts of the Exome Aggregation Consortium and the protein sequence (nonsynonymous, stop-loss, stop-gain, coding indel, frameshift, or splice site variants). Approximately 4000 rare homozygous variants were identified and bioinformatic analyses were performed. Variants with the Combined Annotation Dependent Depletion (CADD) score below 10 were filtered out because these variants were unlikely to affect protein function. In order to reduce the rate of false positive variants and facilitate further genetic testing, we focus on the genes that homozygous variants were identified in 2 to 6 individuals. The remaining candidate genes were then prioritized based on their function (https://www.omim.org) and their expression in artery tissues (https://gtexportal.org). We ended up with 19 rare homozygous variants in 8 candidate genes.

Results: Two homozygous variants in AMOTL2 (Agiomotin-like 2) and COL4A1 (Collagen, Type IV, Alpha-1) were validated by Sanger sequencing, which are potentially involved in the pathogenesis of FTAAD. AMOTL2 is expressed in the dorsal aorta of zebrafish and is part of the anchoring protein of F-actin to the cell membrane for generating junctional force. COL4A1 is expressed in the basement membrane of vessels and multiple mutations identified in this gene have been reported to lead to cerebral vascular diseases. Future protein functional and
clinical studies need to be conducted to validate mutations in these genes for the pathogenesis of FTAAD.