UTHealth™

Medical School

The University of Texas
Health Science Center at Houston

2010 SUMMER RESEARCH PROGRAM
STUDENT ABSTRACTS

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Preface

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

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

To date, more than 1,700 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), National Institute of Neurological Disorders and Stroke (NINDS), and/or by financial support from the Dean and the departments and faculty of the medical school.

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

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

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Acknowledgements

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Lab Research Ownership

Publication and/or Disclosure

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

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

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

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

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ABSTRACT

The role of the caudate nucleus in psychostimulant action

MARYANN U. ABANOBI   *The University of Texas at Houston Medical School*   *Class of 2013*

Attention deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral developmental disorder among children and young adults. One major cause of ADHD is attributed to abnormal dopamine levels in the motive circuit. The psychostimulant methylphenidate (MPD) is the most frequently prescribed drug for treatment of ADHD. MPD increases brain synaptic dopamine concentrations by binding to dopamine transporters and inhibiting dopamine reuptake. Repeated administration of psychostimulants induces behavior sensitization in rats, a condition characterized by increases in locomotor behavior as compared to the initial treatment. Behavior sensitization is an experimental indicator of a drug's potential to elicit addiction/dependence. The goal of this study was to investigate the role of the caudate nucleus (CN), one area of the brain belonging to the motive circuit, on the acute and chronic response to MPD exposure using an open-field assay. Twenty-two adult Sprague-Dawley rats were randomly assigned to three groups: an intact control group, a CN sham-operated group, and a CN bilateral electrical lesion group. On day 1, baseline behavioral activity was recorded for 1 h, followed by surgery for the sham and lesion groups and 5 days of recovery. On the 8th day, additional baseline was recorded followed by 6 days of MPD (2.5 mg/kg i.p.) injections, a 3 day washout period and a rechallenge with the same MPD dose on the last day. All three groups showed increases in behavioral activity after acute MPD exposure. Chronic MPD exposure elicited behavior sensitization in both the sham group and control groups, but failed to elicit behavior sensitization in the CN lesion group. These results suggest that the CN plays a role, at least in part, in the expression of behavior sensitization due to chronic MPD exposure.

ABSTRACT

The role of nucleus accumbens dopamine terminals in Ritalin (methylphenidate) function.

BENJAMIN M. AERTKER   *The University of Texas at Houston Medical School*   *Class of 2013*

Methylphenidate (MPD) is the most commonly used drug to treat attention deficit-hyperactivity disorder(ADHD), one of the most prevalent behavioral disorders afflicting children and young adults. MPD is regularly misused or diverted to other individuals. Previous studies have shown that chronic administration of MPD can cause sensitization, an experimental marker for drug dependency. Recently, it was determined that electrical lesions of the nucleus accumbens(NAc) lead to an exaggerated acute response to MPD. The objective of this study was to determine what role dopaminergic nerve terminals in the NAc have on the acute and chronic effects of MPD by targeting them for selective bilateral destruction with 6-hydroxydopamine(6OHDA). 23 male Sprague-Dawley rats were divided at random into 3 groups: control, sham operated and bilateral 6OHDA lesioned NAc. Baseline activity of the animals was recorded prior to surgery and again after five days of recovery. The animals were then administered 2.5mg/kg of MPD for 6 days. Following a washout period of 3 days, the animals were rechallenged with 2.5mg/kg of MPD. The acute effect of MPD was marked by an increase in locomotor activity($p<0.05$) in all 3 groups. After the MPD rechallenge, 6OHDA lesioned animals exhibited significantly greater locomotor activity when compared to controls ($p<0.05$) and a nonsignificant increase over shams. The 6OHDA lesioned animals also appeared hypoactive when compared to both control and sham lesioned animals on the first day of washout. These results suggest that lesions of the NAc by 6OHDA resulted in enhancement of the chronic effects of MPD treatment.

ABSTRACT

Differential Efflux of the Fluorescent Vital Dye, Rhodamine 123, Identifies Functionally Distinct Subpopulations of Mesenchymal Stem Cells *In Vitro*

BRIAN A. BLAUGRUND   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Paul J. Simmons, PhD; Institute of Molecular Medicine
Supported by: Paul J. Simmons, PhD; Institute of Molecular Medicine
Key Words: mesenchymal stem cell, rhodamine 123 efflux, bone marrow

Bone marrow (BM) stromal cells, commonly known as mesenchymal stem cells (MSCs), are routinely isolated via plastic adherence for growth in culture. The resulting heterogeneous population contains a primitive subpopulation that is currently unidentifiable. The fluorescent vital dye, rhodamine 123 (Rh123), has been used previously to isolate enriched populations of hematopoietic stem cells (HSCs) from BM, but its utility for identifying MSC subpopulations has not been tested until now. Primary cultures of murine MSCs were incubated in Rh123 solution to promote uptake and then allowed to efflux over various timeframes. Following efflux, they were separated by flow cytometry into dye-retaining (Rh123^{BRIGHT}) and dye-effluxing (Rh123^{DULL}) subpopulations. These subpopulations were assayed in vitro for multi-lineage differentiation potential. Both subpopulations demonstrated osteogenesis, adipogenesis, and chondrogenesis. Rh123^{DULL} cells consistently numbered 5% or less of the total viable MSCs and exhibited a small, agranular morphology, according to light scatter. In contrast, the size of Rh123^{BRIGHT} cells was indistinguishable from the majority of MSCs. Re-staining of expanded Rh123^{DULL} cells showed that the Rh123^{DULL} phenotype was maintained in vitro. On the other hand, re-staining of expanded Rh123^{BRIGHT} cells showed no generation of the Rh123^{DULL} phenotype in vitro. Verapamil, which blocks Rh123 efflux in HSCs, failed to block efflux in MSCs. Thus, the efflux mechanism in HSCs and MSCs appears to be different. Finally, Rh123^{DULL} subpopulations were identified in rat, sheep, pig, and human BM cultures, suggesting that Rh123 efflux may be a practical new way to identify hierarchically primitive mammalian MSCs in vitro.

ABSTRACT

Study to Assess the Effects of Total Intravenous Anesthesia with Propofol/Remifentanyl Compared to Sevoflurane/Remifentanyl for Endoscopic Sinus Surgery: Novel Approach

MARK R. BOMBULIE   *The University of Texas at Houston Medical School*   *Class of 2013*

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

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

Key Words: Total intravenous anesthesia, endoscopic sinus surgery

Endoscopic sinus surgery (ESS) has been crucial in the surgical treatment of chronic sinus disease, permitting outpatient sinus surgery with minimal morbidity. A critical factor in ESS is the amount of blood in the surgical field. Because propofol suppresses cardiac output more than sevoflurane, the use of propofol as total intravenous anesthesia (TIVA) might reduce the amount of intraoperative blood loss compared to of sevoflurane, an inhalation anesthetic. Patients undergoing ESS were randomized to receive either TIVA or sevoflurane. Blood flow to the sinuses was measured in optical densities (O.D.) using the Rhinolux system, which utilizes light absorption similarly to pulse-oximetry. Before induction, the baseline nasal mucosa blood flow was measured and assigned a value of 0 O.D. Values were measured every 0.5 seconds, and averaged for the surgery. Patients on TIVA had an average blood flow of -0.196 O.D. +/- 0.311, and patients receiving sevoflurane had an average blood flow of -0.132 O.D. +/- 0.150. The patients on TIVA showed a greater reduction in blood flow, but a two-tailed t-test demonstrated the results as not significant ($p=0.667$). Blood loss was measured using the Neptune Waste Management System, which measures the volume of fluid suctioned from the field. TIVA patients lost 193+/-231 ml of blood, while inhalation patients lost 285+/-460 ml of blood. TIVA patients had less blood loss, but a two-tailed t-test showed the results to not be significant ($p=0.698$). In conclusion, there appears to be no significant benefit from using TIVA over inhalation anesthesia during endoscopic sinus surgery.

ABSTRACT

Personalized Molecular Targeted Therapy for Renal Cell Carcinoma Based on Morphoproteomics

JEFFREY P. BREKKE   *The University of Texas at Houston Medical School*   *Class of 2013*

Current treatment options for renal cell carcinoma utilize the specific molecular targeting ability of Sorafenib, Sunitinib, Pazonpanib, Everolimus, and Temsirolimus as well as off-label use of other FDA approved drugs such as Metformin, Melatonin, and Thalidomide, which target specific pathways involved in angiogenesis and cell proliferation. Oncologists are faced with a difficult decision in choosing which drugs to use in targeting each individual patients tumor. By physically identifying the specific pathway associated with each biopsy, also known as morphoproteomic analysis, it is plausible that the most aberrant pathways can be identified and treated with the most efficacious drug based on molecular targeting algorithms. It is also thought that if a patient's disease progresses, a new biopsy can be performed to identify the new aberrant pathway to be targeted by appropriate therapy.

The patient population consisted of RCC Patients who presented to the clinic as candidates for morphoproteomic analysis based therapy on and after 7/2009. Thirty one patients, average diagnostic age of 56.1 years, received morphoproteomic analysis of a primary biopsy, metastatic site, or both depending on the accessibility of sections. All prior and current treatments, duration of treatment, and whether each treatment was based on morphoproteomics was recorded. Chemistry and hematologic studies were performed at the beginning of each morphoproteomics based therapy.

Of the 19 males and 10 females, primary histology reports we accessible in 20 patients. The majority of patients presented with at least stage 3 RCC of clear cell type and an average primary tumor size of 10.0 cm. Twelve patients had evidence of metastasis at the time of diagnosis. The causes for termination of prior treatment ranged from adverse side effects, completion of drug trial, or progression of disease. Patients received more than one treatment, and the average duration of treatment was 8.8 months. Morphoproteomic based therapy was terminated in only 4 patients during the short duration of this study, with an average duration of treatment of 3.4 months for those terminated.

The data suggest that oncologists can use morphoproteomic analysis of biopsies in conjunction with molecular targeting algorithms when deciding treatment for each individual patient. Whether this method of treatment significantly improves outcomes in patients with advanced RCC Compared to current empiric treatment decision is yet to be determined.   Randomized study of a longer duration would provide better insight into the efficacy of morphoproteomics.

ABSTRACT

Restitution of Pulmonary and Intestinal Syndecan-1 after Hemorrhagic Shock by the Use of Fresh Plasma

RYAN M. BROWN   *The University of Texas at Houston Medical School*   *Class of 2013*

INTRO: Hemorrhagic shock (HS) is the most common cause of potentially preventable death after both civilian and combat traumatic injury. We and others have recently demonstrated that high plasma:RBC ratios in massive transfusion following HS is beneficial for preventing death. In this study, we investigate the effect of plasma resuscitation on syndecan-1, a glycocalyx protein important in inflammation and barrier function, in the lung following hemorrhagic shock. We also investigate the effect of plasma age on syndecan-1 restitution. **We hypothesize that resuscitation with Day-0 fresh frozen plasma (FFP) will reduce injury and minimize the loss of syndecan-1 from pulmonary epithelium.**

METHODS: Using a coagulopathic mouse model of hemorrhagic shock (MAP of 35±5mmHg), mice received either no resuscitation (Shock), Lactated Ringer (LR), Day 0 plasma (PLS-0), or Day 5 plasma (PLS-5) resuscitation and compared to shams. After 3 hours, mice were sacrificed and lungs harvested. H&E stain was performed to assess injury and myeloperoxidase (MPO) activity assay was performed to assess polymorphonuclear leukocyte (PMN) infiltration. Immunofluorescent staining for syndecan-1 was performed to evaluate syndecan-1 expression in lung tissue.

RESULTS: Animals resuscitated with Day 0 plasma demonstrated significantly less lung injury and inflammation compared to animals resuscitated with day 5 plasma, lactated Ringers, and shock alone. Immunostaining suggested that day 0 plasma maintained sydnecan-1 expression after shock. Similar findings were also shown in the gut.

CONCLUSION: This data suggests that fresh (day 0) plasma protects against lung and gut injury and inflammation after hemorrhagic shock, which may be related to restitution of syndecan-1. Further investigation is warranted to determine if this protective effect translates into reduced mortality for patients sustaining severe injury and requiring massive transfusion.

ABSTRACT

Outcomes of Preemptive Colostomy in Patients with Low Rectal and Anal Tumors

JOHN BURLESON   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Stefano Millas, MD, Department of Surgery
Supported by: Department of Surgery

To retrospectively review the outcomes in patients with low rectal and anal carcinoma who were initially managed with diverting colostomy or ileostomy prior to any neoadjuvant or surgical therapy. In addition, to evaluate what clinical, radiographic, and endoscopic criteria are involved in deciding whether or not to divert the fecal stream prior to initiating therapy. The hypothesis to be tested is that preemptive colostomy allows a greater proportion of patients to complete chemotherapy and radiation, while minimizing tumor associated morbidity, compared to non-diverted patients with similar tumor characteristics. Colostomy associated morbidity will also be evaluated. In other words, is the morbidity associated with allowing the fecal stream to continue normally (with risk of possible obstruction etc.) which could jeopardize the continuation of chemotherapy and radiation treatment higher than the morbidity associated with the added surgical intervention(s) required to divert with an ostomy.

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ABSTRACT

Outcomes of Preemptive Colostomy in Patients with Low Rectal and Anal Tumors

SEAN BURY   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: David Wainwright, MD, Department of Surgery

Supported by: Department of Surgery

Key Words: Re-epithelialization, nonhomogeneous, epithelia buds

Quantification of re-epithelialization is necessary to determine optimal wound therapy. Current methods are insufficient and unscientific. Our method tracks re-epithelialization following partial thickness burns from two sources: skin on the periphery of the wound and viable epithelial cells inside hair follicles and sweat and sebaceous glands. We aim to establish the rate of re-epithelialization of partial thickness burns at different anatomic sites. Partial thickness burn sites were photographed at 24-hour intervals over the period of patient hospitalization. Photos of the same sites were compiled in a series. Wound margins and "epithelial buds were traced and quantified using Image J software.

Data has been analyzed from 22 patients using our technique. Average age was 43 yrs (17-66) and burn size 19.5% (10-40%). The initial island count varied from 16 -108 per wound depending on the burn location and depth. The number initially increased as new units produced epithelium and then remained constant until 50% wound closure was attained at which time the units began to coalesce. The island diameter increased from 0.183 mm2 (range 0.06 - 0.364 mm2) to a point at 75% closure when individual islands were difficult to identify. The rate of re-epithelialization (8% per day (range 1.3 to
17.9%)) and day to 95% wound closure was highly variable, reflecting the nonhomogeneous patient and burn characteristics. Differing rates can be attributed to wound depth, skin thickness and vascularitydifferences. Statistically significant data will be generated as study is continued.   Further studies will aim to standardize the method of photography and seek to establish the rate of re-epithelialization on a larger patient population.

ABSTRACT

Underestimated Gastrointestinal Dysmotility in Pediatric Mitochondrial Disease Patients

SAMUEL W. CARSON   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Kuojen Tsao, MD, Department of Pediatric Surgery
Mary Kay Koenig, MD, Department of Pediatrics

Supported by: University of Texas at Houston Medical School–Department of Pediatric Surgery
University of Texas at Houston Medical School-Office of the Dean

Key Words: Mitochondrial disease, gastrointestinal surgery

Pediatric mitochondrial disease encompasses a group of disorders that most commonly present as neurological manifestations. However, gastrointestinal symptoms have been reported as high as 15%. Although poorly described, these conditions often result in GI-related surgery. We hypothesized that the impact of GI related procedures is underestimated.

A retrospective review of patients under the age of 18 at a tertiary referral center for pediatric mitochondrial diseases was performed. Primary outcome variable was GI-related operations. Demographic and disease-related data were collected along with other data concerning surgical procedures.

We identified 91 confirmed pediatric mitochondrial disease patients, of which 33 (36.3%) had undergone gastrointestinal procedures. A total of 73 surgeries were performed with a median age of 3.6 years (range 8 months – 15 years) at the time of the first procedure with of median of 2 operations per patient (range of 1-10). Operations included: 17 (78.8%) gastrostomies, 11 (33.3%) gastrostomies with fundoplication, 3 pyloroplasties (9%), 5 received gastro-jejunostomies (15.2%), 2 jejunostomies (6%), 7 GI biopsies (21.2%), and 2 colostomies (6%). Of those patients, 24 (72.7%) underwent one or more GI-related procedure before diagnosis of mitochondrial disorder.

Children with mitochondrial disease have a high incidence of gastrointestinal procedures, many (72.7%) before their mitochondrial disorder is diagnosed. These appear to be related to upper GI dysmotility. Patients with neurological disorders with persistent GI symptoms, despite escalating interventions, may benefit from early mitochondrial disease testing.

ABSTRACT

Primary care providers' experiences with weight loss resources

MONICA C. CHEN   *The University of Texas at Houston Medical School*   *Class of 2013*

Establishing partnerships between weight control programs and primary care physicians (PCPs) could offer a substantial public health benefit. As such, it is critical to learn how PCPs view these programs if such weight control programs are to be linked with primary care practices. Therefore, we conducted 3 focus groups with 5 – 7 internal medicine and family medicine physicians from UT Houston (n = 18) to explore their experiences and attitudes regarding certain weight control programs and provide the groundwork for future research on the incorporation of weight loss resources into the primary care setting. Focus group discussions were recorded and transcribed verbatim. Transcripts were reviewed iteratively for themes. The PCPs focused on affordability, structure, familiarity, practicality and educational value when evaluating or suggesting different weight loss resources to their patients. Cost was the dominant consideration– i.e. the PCPs were concerned about recommending weight control programs that the patients could afford. Additionally, patients' education, motivation, and environment shaped participant experiences and success in helping patients lose weight. While structured programs and specialists were often cited as common resources, PCPs reported that they typically tried to provide patient education and motivation. Experience with online weight loss programs was limited—with PCPs noting potential benefits (e.g. affordability, support/reinforcement, convenience) while questioning their practicality (e.g. accessibility, lack of coordination, computer literacy prerequisite). PCPs frequently expressed frustration with their own limited time as well as with the cultural and economic issues associated with obesity. We will continue to analyze the current data and will also conduct focus groups in other geographic locations to explore PCP experiences and attitudes towards weight loss resources.

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ABSTRACT

Investigating the Role of CD300G in Immune Complex Processing by the Kidney

ZACHARY R. COMPTON   *The University of Texas at Houston Medical School*   *Class of 2013*

Immune complexes (IC) are formed from the binding of antigens by specific antibodies. Deposition of IC is a factor in many inflammatory disorders such as glomerulonephritis and systemic lupus erythematosus. Previously CD300g was identified as a candidate receptor for IC on renal endothelial cells (REnCs). The goal of this study was to investigate the importance of CD300g in kidneys in a mouse acute immune complex model. CD300g KO mice were compared to C57BL/6 littermates, both untreated and after injection of preformed IC, antibody alone or antigen alone. Urine was collected for measuring proteinuria, albuminuria, and immunoglobulin excretion. Kidney sections were stained for assessing histology. Lastly, REnC cultures were used to measure cytokine responses to IC. CD300g KO mice had greater baseline degrees of albuminuria and urinary immunoglobulin excretion compared to C57BL/6 mice. Tissue staining suggested modest differences in cellular infiltrates in kidneys of all mice administered IC. After injection of antigen to CD300g KO mice, fewer glomerular leukocytes were detected as compared to numbers detected in C57BL/6 kidneys. After injection of IC, CD300g KO mice had more periglomerular and less intraglomerular leukocytes compared to C57BL/6 mice. Finally, REnCs cultured from CD300g KO kidneys produced less of the chemokine MIP-2 in response to IC. These results suggest that CD300g plays a role in the response to IC by REnCs in vitro and in vivo. CD300g seems to be involved in cellular recruitment to areas of IC deposition in the kidney. In addition, CD300g deficiency may alter the kidney's physiologic handling of immunoglobulin and albumin.

ABSTRACT

A Path to Malignancy: Histone Code Directs Alternative Polyadenylation Site Selection

MARK G. COOPER   *The University of Texas at Houston Medical School*   *Class of 2013*

It has grown clear that mutation of the regulatory regions within the 3' untranslated regions (UTR) of mRNAs contribute to cancer. These locations are prone to mutation, and more dramatically, alternative polyadenylation (APA) at upstream sites can shorten the UTR.

My research effort has been to identify the histone modifications which influence PolyA site selection. Our hypothesis is that histone modification influences cleavage and polyadenylation choice and that these modifications are altered during tumor progression. As a model gene, we chose Cyclin D as it has been found to have altered 3' end formation in transformed cells relative to noncancerous controls. Our experimental approach employed the use of Chromatin Immunoprecipitation (ChIP) using antibodies specific to histone modifications to determine if these modifications are enriched at actively used polyA sites.

ChIP begins by fixing cells, to bind histones to chromatin. The material is sonicated to provide necessary resolution. Gel runs of sonication products demonstrate their size to be in a tight range of 300 to 600 bp. Given that my largest primer set produces 318bp fragments, and that nucleosomes are repeated every 160bp, the size of these chromatin fragments provides confidence that immunoprecipitation with histone antibodies does provide acceptable resolution. These samples were immunoprecipitated with three antibodies: H3K36me3 and unmodified H3, to determine the relative level of modification, and IgG as control. Early runs of RT-PCR demonstrate the expected correlation as the U2OS cells show an abundance of H3K36me3 present at the proximal APA site. This is consistent with previous findings that U2OS has mixed expression, representative of the proximal and distal APA sites.

After demonstrating this correlation, we intend to study a mechanism of action that would strengthen our findings. By up-regulating a methyl transferase enzyme, we expect to induce novel histone trimethylation. We expect this to lead cells to prefer a proximal APA site. During the course of my work, I gained proficiency in designing primers and have begun characterizing the ERCC6 gene which is involved in excision repair and also has known APA site selection.

ABSTRACT

Molecular analysis of fresh blood and fresh and archival tissue specimens from prostate cancer patients

ANDREW J. COYNE   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Robert Amato, DO, Department of Oncology
                Gurjyot Doshi, MD, Department of Oncology

Prostate cancer is the second most deadly cancer in men in the United States. The lethality of hormone refractory prostate cancer (HRPC) is dependent on its ability to metastasize and adapt over time. Knowledge of the differences in protein expression between archival tissue, metastatic tissue, and circulating tumor cells (CTCs) is desirable to assign molecular targeting agents to inhibit these cellular adaptations. This IRB approved study is a retrospective clinical trial on 20 men with metastatic HRPC treated at the UT Oncology Clinic. Patient tumor assessment consists of Gleason score, tumor markers, serum chemistries, metastatic tumor burden, CTC count, number of prior therapies, and proteomic analysis of a metastatic biopsy. The study is ongoing, as 6 more patients are pending to be enrolled in the study, and 5 more eligible patients need to be identified to bring the total number of subjects up to 20. The biopsy reports of the metastatic tissues are also still pending. Once the biopsy reports are complete, we will see if there is any correlation between the clinical severity of the disease and the expression of specific biomarkers, along with the effectiveness of molecular targeting agents signified by a reduction or stabilization of tumor burden and tumor markers.

ABSTRACT

Infection rates in delayed and acute repair of tibial plafond fractures

JACOB T. DAVIS   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Kyle F. Dickson, MD, Department of Orthopaedic Surgery
Supported by: Kyle F. Dickson, MD and The University of Texas at Houston Medical School
               Department of Orthopaedic Surgery
Key Words: Plafond, pilon, infection, staged repair

Tibial plafond fractures involve the distal articular surface of the tibia and are also referred to as pilon fractures, due to the hammering force associated with these fractures. Open reduction, internal fixation (ORIF) of the tibia allows for direct visualization of the plafond, permitting the best anatomical reduction of the articular surface, which significantly improves outcomes. However, acute ORIF is not suggested when there is associated soft tissue injury, due to high complication rates. A staged procedure is currently suggested in the literature. It involves acute application of a medial external fixator with possible plating of the fibula to hold length and to provide ligamentotaxis, followed 10-21 days later by a limited ORIF of the articular surface with possible autograft or medial plating at later stages. Our hypothesis is that early ORIF leads to higher rates of infection and worse outcomes while a staged procedure allows for soft tissue healing, reduced risk of infection, and adequate reduction of both the length and articular surface of the tibia. An IRB approved retrospective chart review was undertaken to determine results of plafond fracture repairs. A list of ICD9 code 824 was acquired from the trauma registry and they were graded using the OTA fracture classification. The clinical course was determined for all patients and results analyzed.144 patients were determined to meet the criteria for fracture of the tibial plafond repaired by ORIF, of these 22 (15.3%) became infected directly after closure. Of the most severe injuries, open fractures graded C3 and B3, 6 of 19 (31.6%) of those fixed on or before 4 days after the injury became infect while 2 of 26 (7.7%) those fixed after 4 days became infected. These results were analyzed using a Chi-squared test which yielded a value of 4.054 and a p-value=0.041. This supports our hypothesis that operating in the first four days after injury increases the risk of infection. Fractures of the tibial plafond continue to be difficult injuries to treat with very high infection rates and poor outcomes, but efforts to delay fixation and soft tissue management may improve outcomes in the future.

ABSTRACT

Infection rates in delayed and acute repair of tibial plafond fractures

MELISSA DEFOE   *The University of Texas at Houston Medical School*   *Class of 2013*

Sorafenib is an orally administered medication used in the treatment of renal cell carcinoma that inhibits tumor proliferation, angiogenesis and increases tumor cell apoptosis rates through inhibition of multiple tyrosine kinase activities which indirectly affect the proto-oncogene Ras and vascular endothelial growth factors (VEGFR) -1,-2,-3 and platelet derived growth factor beta (PDGFR- β). The FDA has currently approved Sorafenib to be administered 400 mg PO b.i.d. for the treatment of renal cell cancer. This study will evaluate the effects of dose escalation of Sorafenib on patients with metastatic RCC. 97.3% (n=36) of patients showed an objective response. Patients enrolled in this study showed a positive response with a median PFS of 7 months and a median OS of 35 months. Drug toxicity at 400 mg b.i.d., 600 mg b.i.d. and 800 mg b.i.d. were generally mild to moderate. Hypophosphatemia, the most common higher grade toxicity, can generally be treated with phosphorous replacement. Dose escalation of sorafenib for the treatment of metastatic renal cell carcinoma shows a clear positive response and should be evaluated further.

ABSTRACT

Infection rates in delayed and acute repair of tibial plafond fractures

MICHAEL DISANO   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Nitin Tandon, M.D. Department of Neurosurgery
Supported by: Department of Neurosurgery
Key Words: Tract-based spatial statistics, fMRI

Intro: The purpose of this study was to utilize diffusion tensor imaging (DTI) and Tract-Based Spatial Statistics (TBSS) to evaluate the relationship between language laterality in epilepsy patients measured by the Wada test with asymmetry in measures of fractional anisotropy (FA), of major white matter language tracts. The Wada test is the current gold standard for determining language laterality, but is invasive and costly. Functional imaging techniques require compliant patients, are time-consuming and susceptible to interpretation bias. We have previously shown that it is possible to create a logistic regression model that uses patient handedness, fMRI and arcuate fasciculus (AF) diffusion tensor imaging (DTI) data together to predict language laterality (Ellmore 2010). In this report we try to use imaging and TBSS alone for this purpose. **Methods:** Whole-brain diffusion-weighted images (32-direction, 3T) were obtained on 19 patients without prior resections, scheduled to undergo Wada testing. Individual diffusion-weighted images were non-linearly aligned and transformed into standard patient space using TBSS with a 5mm full-width half maximum (FWHM) variance smoothing (Smith 2006). A group mean FA-skeleton was then constructed from the averaged FA maps and symmetrised. A language dominant minus non-dominant skeleton comparison was made between the hemispheres of the warped individual brains and a one sample t-test for mean > 0 was performed. Voxels were then thresholded for p < 0.01 and voxels of interest in the superior longitudinal fasciculus portion of the AF were selected for generating a volume of interest (VOI). Symmetric VOIs of sampled AF regions were used in both hemispheres. A voxel-based analysis of FA in the individual non-linearly aligned space and computation of a laterality index (LI) where LI = [(Left average FA - Right average FA) / (Left average FA Right average FA)] * 100 was then carried out. **Results:** Wada testing revealed that 15 patients had L sided language and 4 patients had R sided language). Of these 19 patients, our method predicts Wada laterality outcome in 18, the remaining patient was non-classifiable (-5 < LI < 5). This analysis shows that an area of language dependant, very significant hemispheric white matter asymmetry exists in the superior longitudinal fasciculus (SLF). Probabilistic tractography constrained by the VOI in individual patient space demonstrates that this contributes to the SLF portion of the AF.
Conclusions: Based upon this study, we conclude that DTI and TBSS may be a useful tool for predicting language laterality in patients with epilepsy. The availability of DTI makes this method easy to carry out. Analysis of asymmetry of major language related white matter pathways allows for a non-invasive method for reliably predicting language laterality. Future exploration includes extending this measure of analysis to other white matter markers of integrity including mean diffusivity, extending this method to patients who have cortical stimulation mapping and confirmation of the finding in larger numbers.

ABSTRACT

A retrospective analysis of the Vitamin D status of orthopaedic trauma patients

David Booty Doherty, Jr.   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Catherine G. Ambrose, PhD, Department of Orthopaedic Surgery
Supported by: The University of Texas Medical School at Houston office of the Dean, and The department of Orthopaedic Surgery
Key Words: Vitamin D, trauma, 25-OHD, fracture, orthopaedics

Recent research has repeatedly demonstrated that vitamin D status is associated with many health outcomes, and interconnects the digestive system, musculoskeletal system, and immune system. Vitamin D status in a trauma population has not been reported and insights could provide a novel tool in prevention of complications such as nonunion and osteomyelitis. The incidence of vitamin D insufficiency or deficiency in a level 1 trauma center in the Texas Medical Center in trauma patients with an open or closed fracture of any type was assessed. As part of a newly instituted trauma protocol, chemiluminescent immunoassay determination of serum 25-hydroxyvitamin D (25-OHD) level was performed on patients necessitating orthopaedic trauma care. The charts of patients admitted between June 2009 – July 2010 greater than 18 years old with an ICD9 fracture diagnosis were reviewed. Data concerning medications, medical history and general demographics, including, age, date of admission, gender and ethnicity, were obtained from hospital charts. Vitamin D levels between 20 and 30 ng/ml were recorded as "insufficient," and levels below 20ng/ml were classified as "deficient", while levels above 80ng/ml were considered "high". A total of 42 patients were identified who met the above inclusion criteria. 21 males and 21 females were identified and had a mean age of 60 ± 21 (range 20-102). 4 patients had sufficient levels of Vitamin D, while 21 were deficient, 16 were insufficient, and 1 was high. Based on Pearson Chi-squared analysis, there were significantly more patients deficient than sufficient and insufficient than sufficient ($p<0.05$). This significance was also observed within male and female subgroups, and for any time year. There was no subgroup that had a significantly larger amount of patients with deficient, insufficient, or sufficient vitamin D levels. This data clearly shows the high incidence of low vitamin D levels within a large trauma population. Initial lab miscommunication has been clarified, and will allow this research to benefit from a much larger sample size. A further prospective investigation to determine if there are negative health ramifications for fracture patients associated with deficient or insufficient vitamin D levels is also warranted.

ABSTRACT

3T MR imagining as an accurate tool for use in clinical decision making for treatment and identification of prostate cancer recurrence

SCOTT ELLSWORTH   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Robert J. Amato, DO, Dept. of Internal Medicine, Director Division of Oncology
Supported by: The University of Texas at Houston Medical School, Robert J. Amato
Key Words: Prostate, MRI, Biochemical relapse, prostatectomy, radiation

Background: Currently, prostate specific antigen (PSA) level monitoring with digital rectal exam (DRE)is a proven screening tool for early detection of prostate cancer, but it is associated with high rates of overdiagnosis and hence overtreatment. Imaging modalities are being looked to as a potential way to enhance detection in the pelvis. MRI has been targeted because of its ability to accurately differentiate between normal and cancerous tissue, especially with when used in combination with functional imaging techniques. This study assessed the accuracy of MRI in detecting prostate cancer in the pelvis in three different patient populations. **Methods:** A retrospective chart review of an ongoing patient population was conducted. Subjects were selected from the Division of Oncology at the University of Texas Medical School at Houston outpatient clinic. Patients who had an MRI evaluation during the course of their treatment for prostate cancer were included in the study.   The first group of patients was undergoing treatment prior to a planned prostatectomy. Baseline and follow up data were obtained for comparison. The second group had a history of radiation to the prostate with a later rise in PSA levels. The third group had a history of prostatectomy with a later rise in PSA levels. For these two groups, MRI evaluation was correlated with subsequent biopsy, if indicated. **Results:** In the first group, 6 patients had MRI evaluation, and all 6 had positive correlation between MRI and biopsy findings, showing that MRI is accurate in detecting cancer. In the second group, 3 of 11 patients had positive MRI findings. Of the 3 with positive scans, one correlated with biopsy results, one did not, and the results of the third biopsy are pending. In the third group, 1 of 17 patients had a positive scan, but the biopsy results for correlation aren't yet available. **Conclusion**: As this is an ongoing study, no conclusions can be drawn at this time, however, the results of group 1 indicate that MRI may prove a useful clinical tool. Further research is needed to truly assess the usefulness of MRI.

ABSTRACT

Postoperative Speech Evaluations in Patients with Cleft Palate: A 12 Year Retrospective Study

Michael A. Evans   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: John Teichgraeber, MD, Department of Pediatric Surgery
Supported by: John Teichgraeber, MD, Department of Pediatric Surgery
Key Words: Palatoplasty, Palatoschisis, VPI, Cleft Palate, Speech Pathology

The main goals of a primary palatoplasty are closure of the communication between the oral and nasal cavities, along with providing a foundation for normal speech. However, after surgery, complications may exist, including fistula or velopharyngeal incompetence [VPI]. Success of palatal surgery is dependent on development of normal speech. In all cases, speech therapy is required by the patient. The purpose of this study was to investigate the speech results of patients treated for cleft palate, and to compare those results based on each patient's type of cleft and which procedure was utilized to correct it. Over 12 years [1992-2004], Dr. John Teichgraeber performed 148 primary palatoplasties on consecutive patients with cleft palate. Many of these procedures required secondary correction to achieve proper speech. The first step involved a chart review of all patients with cleft palate that underwent primary palatoplasty. Each case was reviewed on the basis of whether a secondary procedure was necessary, when that procedure was necessary, and why it was necessary. After timing and causality were determined, the gender of the patient, and the age of the patient at the time of the primary palatoplasty were considered. The end date of 2004 was selected to allow for proper follow up, allow for a secondary procedure when needed, and to ascertain the outcome of that secondary procedure. This lapse was estimated to be 5 years by the physician. After data is tabulated, a multiple regression will be computed. The dependent variable will be the result of speech evaluation [good or bad]. The independent variables will be the type of cleft [bilateral or unilateral], the severity of the cleft [complete, incomplete, soft palate only, or bifid only], the surgical procedure used to treat the patient [palatoplasty only, palatoplasty plus postpharyngeal flap, or palatoplasty plus lateral pharyngeal flap], gender of the patient, and age of the patient at the time of primary surgery.

ABSTRACT

Effect of Point mutations within AtxA, the Master Virulence Gene Regulator of *Bacillus anthracis*

RICARDO GARCIA   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Theresa Koehler, Ph.D. Department of Microbiology & Molecular Genetics

Bacillus anthracis, the causative agent of anthrax, regulates production of the anthrax toxin and other virulence factors via the anthrax toxin activator, AtxA. The protein is crucial for toxicity of the bacterium as the removal of the *atxA* gene renders *B. anthracis* avirulent; however the protein's mode of action is still not entirely understood. Currently, we hypothesize that AtxA has two functional regions: a DNA-binding domain within the amino-terminus and a regulatory region near the carboxyl-terminus. Data from previous experiments indicate that cysteine residues may play a role in AtxA function. Our project focuses on independently substituting each of the six cysteine amino acids in AtxA for serine residues and studying the effect of each mutation on AtxA activity. To analyze *B. anthracis* encoding each mutated protein, the strains were cultured in toxin-inducing conditions and samples were taken for Western blot and β-galactosidase analyses. From these experiments we can assess the level of AtxA produced and the activity of AtxA, respectively. Substitution of the cysteine amino acids resulted in no change, a loss-of-function, or a gain-of-function phenotype when compared to the native protein. Mutations located in the DNA binding region (C96S and C161S) produced the most severe decreases in AtxA activity. Most of the cysteine substitutions in the regulatory region of AtxA (C202S, C356S, and C370S) had little effect on AtxA activity, whereas one mutation (C402S) produced a gain-of-function phenotype. Finally, we investigated the effect of each cysteine mutation on the oligomeric state of AtxA.

ABSTRACT

Improving Early Prediction of Neurocognitive Impairments at Preschool and School age in Preterm Infants Through Advanced MRI

EMILY C. GRIMSHAW   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: **Margarita** Jimenez, MD, MPH, FAAP, Department of Pediatrics
Jon E. Tyson, MD, MPH, Department of Pediatrics
Supported by: The University of Texas at Houston Medical School
Key Words: ELBW, neurodevelopmental outcomes, VMRI

The high-risk nature of extremely low birth weight (ELBW: $\leq$1000 g) infants is evident in MRI studies, with >80% demonstrating abnormal brain development and/or injury prior to NICU discharge. This study will examine the effects of ELBW and neonatal intensive care on detailed macrostructural, microstructural and metabolic measures of abnormal brain development and injury on advanced MRI findings and on neurodevelopmental outcomes. A cohort following of 121 consecutively born ELBW survivors from 2005 to 2007 and 20 healthy term controls will undergo neurodevelopmental testing at 5 years and again at 7 years in an effort to develop accurate prediction models of neurocognitive outcomes based on an extensive database of perinatal and neonatal risk factors collected at pre-NICU discharge at term-equivalent age. In addition, high-quality anatomic MRI, volumetric MRI (VMRI), diffusion tensor MRI (DTI), and magnetic resonance spectroscopy imaging (MRS) data obtained pre-NICU discharge will be correlated with developmental testing outcomes. We seek to determine whether 1) the combination of perinatal/neonatal risk variables and any finding of moderate-severe brain injury on anatomic/advanced MRI at term-equivalent age in ELBW infants predicts the composite outcome of neurosensory, cognitive, motor, verbal and social impairment at 5 and 7 years of age; 2) specific combinations of regional volume and diffusion abnormalities found through VMRI and DTI will predict individual impairments.

ABSTRACT

Antibodies against Epstein-Barr Virus in Multiple Sclerosis

MARY S. GUIRGUIS   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: J. William Lindsey, MD, Department of Neurology
Supported by: The Consortium of Multiple Sclerosis Centers
Key Words: Multiple sclerosis, Epstein-Barr Virus

Multiple sclerosis (MS) is thought to be an immune-mediated disease. A characteristic feature of MS is the presence of oligoclonal immunoglobulin (IgG) in the cerebrospinal fluid (CSF). The target of this IgG is not known. Studies have shown evidence that Epstein – Barr Virus (EBV) infection is associated with MS. The hypothesis of this study is that the IgG response in the CSF of MS patients is directed against EBV-infected cells and specific for EBV proteins. The B95.8 cell line is an EBV-infected marmoset cell line which produces high amounts of virus. Soluble protein from infected cells and cell-free virus protein were each extracted from B95.8 cells, following five days of PMA stimulation to maximize virus production. Extracted soluble cell protein was immunoprecipitated with CSF from 24 MS patients and 24 controls. Precipitated protein was run on 4-12%gradient bis-tris gels. The same CSF samples were tested in ELISA assays using either soluble cell protein or cell-free virus protein bound to plate. In immunoprecipitation experiments, some samples showed a band at approximately 45 kD. This band was excised and identified as actin by mass spectroscopy. In ELISA assays, we observed a trend for higher binding to both soluble cell protein (p=0.0526) and cell-free virus protein (p=0.111) when compared to controls. Binding to cell-free virus protein was higher than to soluble cell protein. In addition, binding to soluble cell protein and cell-free virus protein were positively correlated (r=0.874). We conclude that there is a trend for higher IgG specific to EBV in MS. Testing a higher number of CSF samples would be the next direction to confirm these results.

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ABSTRACT

Outcome of Medial and Lateral Plating Recalcitrant Distal Femur Non-Union Fractures

BRYAN D. HANUS   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Milan Sen, M.D., Department of Orthopaedic Surgery

Supported by: Catherine Ambrose, PhD, Department of Orthopaedic Surgery
               Mark Brinker, M.D., Fondren Orthopedic Group, Joe King Orthopedic Institute
               Daniel O' Connor, PhD, Department of Health and Human Performance ,
               University of Houston

Key Words: Distal, Femur, Non-union, Double Plate, Duel Plate

Non-union of fractures of the distal femur are one of the most difficult problems to treat in orthopedics due to difficulty in achieving adequate fracture stabilization. Multiple studies have been conducted that utilized various surgical techniques in an attempt to heal this fracture, but most of these techniques did not achieve consistent results. Therefore, no consensus currently exists as to the most effective way to repair this type of fracture. The purpose of this study is to evaluate the efficacy of surgically treating recalcitrant distal femur non-unions using medial and lateral locking plates supplemented with autogenous bone graft. This prospective study is part of a larger, ongoing orthopedic outcomes initiative at the facility. Eight consecutive patients with distal femoral non-unions who were treated with dual locking plates and autogenous bone grafts by one surgeon between June 12, 2007 and June 28, 2010 were included in the study. All of the patients had at least one prior failed attempt at fixation of the non-union before treatment. Medical records were reviewed to obtain age at presentation, time between injury and referral, prior surgeries, co-morbidities, and other patient-specific variables. The primary outcome measures of the study are days until radiographic evidence of bone union and change in SF12, AAOS Lower Limb Core scale, Time Tradeoff and Brief Pain Inventory scores following treatment. Time until bone union data was compared to other published data to evaluate effectiveness of treatment. This is an ongoing study as final follow-up data are currently being collected and analyzed.

ABSTRACT

Temporal Expression of the ApC/EBP Transcription Factor

GEORGE HEBERTON   *The University of Texas at Houston Medical School*   *Class of 2013*

Aplysia californica has long served as an animal model for investigations into the biochemical mechan
underlying learning and memory. Recent research has revealed the importance of the CCAAT enh
binding protein (C/EBP) in the formation of long-term memory. My research was designe
characterize the temporal expression of ApC/EBP as a means to better understand its role. Neurons
extracted from *Aplysia* pleural-pedal ganglia and stimulated with serotonin, a treatment known to in
long-term memory. These cells and an unstimulated control group were fixed at 1, 5, and 12 h
treated with a primary anti-C/EBP antibody and subsequently with a secondary fluorescently la
antibody. Cells were imaged using confocal microscopy and subsequently analyzed for sta
intensity. No statistically significant differences were found between the groups at any of the time p
These results coupled with poor sensitivity to and specificity for C/EBP on Western blot analysis l
the conclusion that the anti-C/EBP antibody on hand has too poor binding to be of diagnostic u
measuring C/EBP expression. Synthesis of a new, more specific antibody will be necessary to accu
model the temporal expression of C/EBP.

ABSTRACT

Quality of Pre-travel Medical Advice and Impact of Prior International Travel to the Development of Travelers' Diarrhea (TD) in Young Adults From the U.S. Taking Classes in Mexico

HANS B. HEYMANN   *The University of Texas at Houston Medical School*   *Class of 2013*

College students are put at health risk during international study abroad. TD is the most frequent illness acquired during such travel. This study, carried out in language schools in Mexico focused on the quality of pre-travel advice and documentation of TD immunity produced by prior travel to developing countries before this trip to Mexico. METHODS: June to July 2010 U.S. college students attending language schools in Cuernavaca and Guadalajara, Mexico were asked to complete a questionnaire the last week of their stay in Mexico. In the study good pre-trip medical advice was defined as having taken hepatitis A vaccine (HAV). Poor medical advice was defined as taking prophylactic medication to prevent either TD (PTD) or malaria (PM). RESULTS: One hundred twenty six of 249 (51%) students had received HAV. Sixteen (6%) students took PTD and 1 (0.4%) PM while in Mexico. One hundred fifty-four (62%) reported TD. Students who spent at least one week in a developing country in the prior 6 months, 1 year, or 5 years before their current trip did not show reduced rates of TD (P=0.2 to 0.6 for 3 groups). Use of proton pump inhibitors appeared to be related to diarrhea occurrence 11/13 (85%) vs. 143/236 (61%) (P=.14). CONCLUSIONS: Students studying in Mexico are poorly prepared for the health risks of international travel. They experience extremely high rates of diarrhea. Prior visitation to developing countries did not provide protection against TD.

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ABSTRACT

Metformin's effects on the Hedgehog pathway in prostate cancer and neuroblastoma

STEVE J. HONG　　　　　*The University of Texas at Houston Medical School*　　*Class of 2013*

Sponsored by: Priya Weerasinge, MD, MSc, PhD; Department of Pathology and Laboratory Medicine
Supported by: Robert Brown, MD and Maximilian Buja, MD
Key Words: Metformin, prostate cancer, hedgehog pathway, cell death, neuroblastoma

The hedgehog pathway plays a prominent role in bolstering the survivability of various malignancies. Our study was designed to elucidate the involvement of the hedgehog signaling cascade in prostate neoplasia and neuroblastoma, as well as how it relates to the effectiveness of metformin as an anti-tumor agent. Both LnCAP prostate cancer cells and neuroblastoma cells were cultured *in vitro* and treated with metformin in doses ranging from 1 mM-40 mM with exposure times of 24, 48, and 72 hours. Subsequently, proteins were isolated for Western blots and probed with Gli-1, Gli-2, and fatty acid synthase (FAS) antibodies. This technique effectively monitored protein expression. Propedium iodide/Flow cytometry and trypan blue dye were used to quantify cell injury and determine the effectiveness of the drug. The effects of metformin on hedgehog pathway protein expression along with cell injury were visualized via immunohistochemistry. Results of Western blots and immunohistochemistry confirmed our hypothesis that predicted an inverse relationship between amount of hedgehog activity and cell death. Highest concentration of drug ($40\mu M$) proved to inhibit cell growth on culture plates and western analysis of Gli-2 appears to be inhibiting in a dose dependent manner following 48 hour drug exposure where as Gli-1 and FAS appear not to have changed. Molecular characterization of metformin-treated cells could reveal important molecular targets that could potentially be explored to design effective adjuvant therapeutics for neuroblastoma and prostate cancer patients.

ABSTRACT

Depo-provera administration and impact on breastfeeding

HALEY N HORTON   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Pamela D. Berens, MD
                  Obstetrics, Gynecology and Reproductive Services

Key Words: Breastfeeding, Birth Control, Depo-provera

Depo-provera (depot medroprogesterone acetate) is a commonly used form of injection birth control, but it is not yet known how early administration of Depo-provera affects the frequency of breastfeeding or the weight of the infant. Early administration is considered less than six weeks after delivery. Previously, there have been concerns about early introduction of a progesterone birth control interfering with the physiological withdrawal of progesterone after delivery of the placenta. This withdrawal is considered a trigger for maternal milk production. The primary objective of this research study is to determine if there is a difference in milk production when Depo-provera is administrated to mothers within 72 hours postpartum versus 6 weeks postpartum. Women who delivered single infants at term and plan to breastfeed exclusively were eligible for this study. This study was conducted as a randomized and controlled clinical trial at LBJ and Memorial Hermann hospitals. Participating women were divided into two groups: women receiving Depo-provera within 72 hours postpartum and women receiving Depo-provera at the 6 week postpartum visit. Infant birth weight, measurements, and weight at discharge were recorded upon entry into the study, and formula was not given unless medically necessary. Mothers recorded number and volume of breast feedings in a feeding log. Drs. Antoniewicz and Nguyen conducted weekly scripted follow-up telephone calls to gather the information recorded in the feeding logs. Participants in the study are currently still being gathered, and we hope to have results by January 2011. We hope that the results of our data analysis will definitively determine whether or not Depo-provera use at 72 hours postpartum has adverse effects on maternal lactation and therefore infant growth.

ABSTRACT

Acute Stroke Causes Dynamic Changes in Spleen Size Over Time

JAMES PAUL HOVIS,   *The University of Texas Medical School at Houston*   *Class of 2013*

Animal studies have demonstrated that spleen contracts after acute stroke (AS) and contributes to secondary inflammation that increases neurodegeneration; however, there are no known studies on changes in spleen size in patients after AS. Thus, we conducted a prospective pilot study to evaluate whether spleen size changes over time after AS, and if these changes correlated with the severity of stroke. A total of 19 AS stroke patients, 18 years or older and presenting within six hours of onset, in absence of concomitant MI, trauma, autoimmune disease, fever, hypoxemia or hemodynamic instability were enrolled. Demographics, vitals and NIHSS were collected; the first splenic ultrasound (SUG) was performed within six hours of symptom onset and splenic splenic length, width and thickness were measured with hilum as reference point. SUG was repeated once within 24 hours of onset and then daily along with NIHSS until day seven or discharge, whichever was earlier. Splenic volume was calculated and corrected for height, weight and gender using a published formula by Geraghty et al to determine the relative degree of splenic size changes compared to the expected normal range. Splenic volume variation below 15% was considered normal based on five consecutive daily ultrasounds in 8 healthy volunteers. During the study period, a significant increase in mean spleen volume was observed (p-0.037), indicating a period of rapid splenic contraction after the stroke followed by a gradual increase towards the original volume. Three patients exhibited below 15% mean spleen volume change, two of these patients showed significant recovery (NIHSS $\leq$ 1) within a day. Most patients demonstrated spleen contraction either at time of the first ultrasound or in the ensuing 6-24 hour period. Varying degrees of recovery periods were exhibited in the individual patients. Moderate to severe strokes were seen in 9 out of 19 patients; all of these patients exhibited reduction in spleen volume over time. Our results suggest that spleen undergoes dynamic changes in size over time following an acute stroke. There appears to be a correlation of stroke severity with degree of splenic contraction and its return to normal over time; however, further studies are needed to determine the clinical significance of these results.

ABSTRACT

Colonization and dissemination of *Candida albicans* in the mouse gastrointestinal tract

Rachelle M. Jones   The University of Texas at Houston Medical School   Class of 2013

Sponsored by: Michael Lorenz, PhD, Department of Microbiology & Molecular Genetics
Supported by: Michael Lorenz, PhD, Department of Microbiology & Molecular Genetics
Key Words: *Candida albicans*, candidiasis

Candida albicans is a fungal component of the normal flora in the gut, mouth, and vagina. In immunocompromised patients, it can cause disseminated candidiasis by penetrating the gut epithelium. Despite the high frequency of nosocomial infection, little is known about the biology of *C. albicans* in the gut. Objective: This study used mouse models to determine 1) the relative fitness of *C. albicans* mutant strains defective in certain virulence factors and 2) whether *C. albicans* can disseminate from the gut in mice as it does in humans. Methodology: Mice were treated with antibiotics then colonization of the gut was achieved via intragastric gavage, using various mouse strains and antibiotic regimens to determine the optimal protocol. The second aim of this study used an anti-cancer agent to weaken the gut epithelium. Antibiotic-treated mice were inoculated and given an intraperitoneal methotrexate injection, after which dissemination was evaluated via kidney fungal burden. A second experiment using methotrexate was performed in which mice received either wild-type (SC5314) or mutant strains of *C. albicans*. Results: We found little difference in colonization protocol and used ICR mice treated with gentamycin/streptomycin/tetracycline for our studies. Comparison of mutant strain colonization was slowed by technical difficulties in strain construction. Epithelial damage via methotrexate induced significantly higher dissemination relative to control mice. Unexpectedly, mice inoculated with a wild-type strain showed fewer signs of clinical candidiasis in this dissemination model compared to several mutants. Conclusions: Mice can be a valuable model for understanding the biology of *Candida* in the gut.

ABSTRACT

Endotrol tracheal tube assisted endotralheal intubation during video laryngoscopy

Molly A. Keegan   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Carin A. Hagberg, MD, Department of Anesthesiology
Supported by: The University of Texas at Houston Medical School
Key Words: Intubation, stylette, videolaryngoscopy

Patients who are undergoing general anesthesia often have an endotracheal tube placed to assist their breathing. The purpose of this study was to compare the safety and efficacy of traditional endotracheal tube to the Endotrol tube (Covidien, Colorado, USA) using videolarygoscopy. We hypothesized that the Endotrol Tube will be safer and more effective than a traditional endotracheal tube during videolarygoscopy. The study enrolled 60 patients. The patients were randomized into two groups with two subgroups as follows: **Group A** GlideScope® with Endotrol tracheal tube, **Group B** GlideScope® with Gliderite® styletted Endotracheal tube, **Group C** McGrath® with Endotrol tracheal tube, and **Group D** McGrath® with Gliderite® styletted Endotracheal tube. The patients underwent general anesthesia and muscle relaxation before a resident attempted intubation. Intubation time, number of attempts, and ease of intubation were recorded and analyzed. Any complications with either procedure were noted. Patient demographics and difficult airway predictors were similar in all 4 groups. Intubation times were not statistically significantly different for any of the groups. The GlideScope® and McGrath® video larygoscopes usually require a stylette to be used in conjunction with the endotracheal tube during intubation. The study demonstrated that the use of the Gliderite® stylette is safe to use in conjunction with the GlideScope® and McGrath® video laryngoscopes.

ABSTRACT

Intracellular retention of mutant COMP induces apoptotic pathway in murine growth plate chondrocytes

TRUNG B. LE *The University of Texas at Houston Medical School* *Class of 2013*

Sponsored by:	Jacqueline T. Hecht, PhD, Department of Pediatrics Genetics
Supported by:	Shriners, Leah Lewis, Foundation, and NIH
Key Words:	UPR, COMP, Pseudoachondroplasia, ER stress

Pseudoachondroplasia (PSACH) is a severe skeletal dysplasia caused by mutations in the cartilage oligomeric matrix protein (COMP) gene. Mutations in COMP cause improper folding and retention of 97% of the protein in the endoplasmic reticulum. This retention causes ER stress and activates the unfolded protein response (UPR), which is an adaptive response to clear misfolded protein. Studies in rat chondrosarcoma cells transfected with mutant (MT-)COMP showed that increased MT-COMP translation leads to increased accumulation and, along with oxidative stress, favors the apoptotic path. We used our mouse model expressing MT-COMP to further evaluate this finding. Microarray analysis on the growth plate cartilage from 1 month old MT-COMP mice showed higher expression of some of the UPR genes ($p < 0.05$). Here, we used quantitative PCR (qPCR) to confirm those results. Primers were designed for several genes involved in the UPR. cDNA was generated from mRNA obtained from E15.5, 3 week, and 4 week old wild type controls (C57Bl6) and MT-COMP mouse growth plates. Three mice of each type were run in triplicate and HPRT was used to normalize the results. The data were analyzed using T-test statistic. Significant increases in Chop, Atf4, and ero1β was found in the 3 week growth plates. All are important in oxidative stress, which is part of the pro- and apoptotic UPR pathways. This confirms that expression of MT-COMP stimulates the UPR by 3 weeks of age in mice and provides additional evidence supporting the role of apoptosis in the pathogenesis of PSACH.

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ABSTRACT

Computationally Intensive Analysis of Prehospital and ED Data for the Prevention of Overtriage

DANIEL LLOYD MACDOUGALL   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: John B Holcomb, MD, FACS
Supported by: CeTIR
Key Words: Trauma, Triage, Cluster Analysis, Air Ambulance, Emergency Department

BACKGROUND: Overcrowding of Level 1 Trauma Centers leads to congestion and inefficient allocation of hospital resources. Patients arriving by air ambulance are classified as either Code 2 or 3 based on vitals and mechanism of injury. 46% of these Code 2 patients are discharged, and classical statistical analysis of prehospital data fails to predict hospital admission. As physiologic data is abundant and complex, computationally intensive data-mining techniques can help elucidate patterns predictive of relevant clinical outcomes, and present a strategy for triaging patients to a Level 1 or Level 3 trauma center.

HYPOTHESIS: We predicted that k-means cluster analysis of prehospital data and analysis of vitals and laboratory data collected in the emergency department would be predictive of the need for admission.

METHODS: Retrospective analysis of patient records for a random sampling (n=884) of adult trauma patients arriving to MHH by air ambulance from May '07 - May '09. Univariate statistical analysis was performed using unpaired Student's t-test. Multivariable logistic regression modeling was performed and evaluated using the area under the receiver operator curve.

RESULTS: Significant differences between these populations existed for a number of measures taken by EMS. In the ED, decreased temperature, diastolic blood pressure and red blood cell count and increased respiratory rate, and blood urea nitrogen were associated with admission ($.0001<p<.05$) . Cluster analysis failed to provide a reliable predictive model or significantly sized clusters associated with either outcome (area under the receiver operator characteristic curve= .59).

CONCLUSION: While differences exist in the data at these various time points, current analysis does not reveal a reliable and definitive model for admission or discharge. Cluster analysis was able to provide a predictive model better than any single variable, so incorporation into larger model may be warranted.

ABSTRACT

Characterization of Adenylyl Cyclase B by Measurement of Cyclic AMP Levels

WILLIE M. MARQUEZ   *The University of Texas at Houston Medical School*   *Class of 2013*

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

Supported by: The Department of Neurobiology & Anatomy

Key Words: Adenylyl Cyclase, Forskolin, aplB, cAMP

Adenylyl cyclases are a group of important enzymes that convert adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). cAMP has various roles in the cell, although it is most often associated with cell signaling and activation of cAMP-dependent protein kinases. In *Aplysia californica*, there are four known isoforms of adenylyl cyclases (AC): A, B, C, and D. Based on previous studies, the adenylyl cyclase B (aplB) isoform has been shown to play a role in operant learning, which is a process by which the animal learns about the consequences of its actions. In order to better understand aplB and how these signaling pathways are activated, I characterized the activity of aplB *in vitro.* In my experiment, I expected to see a marked increase in cAMP production in those cells over-expressing aplB compared to the cells transfected with a control vector alone. To test this hypothesis, I transfected two groups of Human Embryonic Kidney (HEK) cells: one with a vector containing the *aplB* gene and one with a control vector. Western blot was used to ensure that the protein was present after the transfection procedure. Transfected cells were then treated with forskolin, an adenylyl cyclase activator, and cAMP levels were measured and normalized by amount of total protein. Both the endogenous AC and the overexpressed aplB exhibited a dose response to forskolin, with an appreciable increase over endogenous levels beginning at a concentration of 20 uM forskolin. The difference peaked at about 500 uM forskolin, and the response of aplB began to plateau near 1 mM. These results suggested that there was indeed a dose response to forskolin although the magnitude of the changes were less than expected. Even though western blots indicated that the protein was expressed, the enzymatic activity of aplB may be low in the HEK cells.

ABSTRACT

An Analysis of the Efficacy of a Computer Blinking Software Program

ZANE MARTINDALE   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Dr. Richard Yee, M.D., Department of Ophthalmology and Visual Sciences
Supported by: Dr. Richard Yee, M.D., Department of Ophthalmology and Visual Sciences
Key Words: Computer vision syndrome, blink rate, dry eye disease

Introduction: A pilot study was designed to test the efficacy of a blinking software program in its ability to increase the blink rate in the computer user while minimally interrupting their concentration. The blinking software program has been designed to combat the effects of long-term computer usage among young adults.

Methods: Several individuals were asked to play Solitaire on a laptop computer in an office environment for a period of 15 minutes while their blink rate was being filmed. During the first five minutes, they would play Solitaire without the blinking software prompting any blinking. In the last ten minutes, the researcher turned on the blinking software and continued filming the participant to determine if their blink rate changed. Before and after playing the game they were given a survey to help answer several questions concerning the program's effectiveness. Subjects with dry eye disease as determined by an OSDI score above 35 were excluded. The hypothesis is that if the blinking software were used, it would increase their blink rate and not disrupt their concentration.

Results and Conclusion: As the study has not been approved by the IRB, data collection and a viable conclusion have not been completed at this time.

ABSTRACT

Hemicraniectomy and craniotomy demonstrate similar early outcomes in patients with intracerebral hemorrhage

MEGHAN A. MCINTOSH   *The University of Texas at Houston Medical School*   *Class of 2013*

Intracerebral hemorrhages (ICH) account for 20% of strokes, poor outcomes, and high mortality rates. Surgical evacuation of the clot (hematoma) is of unproven benefit, but is often carried out. While craniotomy + clot evacuation is the current standard in surgical intervention for ICH, hemicraniectomy ± evacuation of the clot may produce less brain disruption, better intracranial pressure, and better outcome. However, little data exist to differentiate the benefits of hemicraniectomy compared to craniotomy. This study compared patients having hemicraniectomy vs craniotomy for ICH at Memorial Hermann Hospital. I retrospectively collected data on ICH cases from August 2004 to April 2010 from a prospectively collected computerized Stroke Registry. Patients with ICH due to aneurysm, AVM, or tumor were excluded. Comparison groups were hemicraniectomy (±clot evacuation) and craniotomy. The primary outcome was the proportion of patients in each group with modified Rankin Scale (mRS) ≤4 at discharge. 64 patients had a hemicraniectomy, 8 of whom had no clot evacuation. 23 patients had a craniotomy. Variables that showed no significant intergroup differences included gender, median NIHSS and GCS on presentation, hemorrhage location and size, both total length of stay and days spent in the ICU, and mRS≤4 on discharge. There was also no difference based on ±clot evacuation. One significant finding was the tendency towards hemicraniectomy in younger patients (52.5 years vs. 59 years; p= 0.055). After using linear regression to correct and match for age and clot size, there remained no difference in mRS outcome. Work is underway to compare 90 day outcomes. In conclusion, this study demonstrated no difference between hemicraniectomy and craniotomy for ICH. Larger numbers of patients, perhaps from a multicentered registry, are needed for further comparison.

ABSTRACT

Does Using LMA Instead of an Endotracheal Tube Affect the Incidence of Postoperative Vomiting in Children Undergoing Strabismus Correction

DMITRIY MESHKOV   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Samia Khalil, MD, Department of Anesthesiology

Supported by: Samia Khalil, MD, Department of Anesthesiology

Key Words: LMA, endotracheal tube, strabismus

The purpose of this study is to compare the laryngeal mask airway (LMA) to the endotracheal tube (ETT) with respect to the incidence of postoperative vomiting (POV) in children undergoing strabismus correction. The etiology of postoperative nausea and vomiting is multifuctorial. Among these factors, the afferent stimulation of the pharynx may be impacted based on LMA or ETT tube usage.

To be eligible for the study, children needed to be between the ages of 2 and 12, have an ASA classification of 1 or 2, and be scheduled for elective, outpatient strabismus correction. After pre-medication with midazolam (0.5mg/kg), anesthesia was induced via mask and consisted of sevoflurane, air, and oxygen. Propofol (2mg/kg) and fentanyl (2mcg/kg) were administered to facilitate ETT or LMA placement. The incidence of POV was monitored for 24 hours following the conclusion of anesthesia administration.

The incidence of POV using the ETT is approximately 50% or more in this study population. A sample size of 103 will be able to detect a 20% difference between groups with 5% significance and 80% power using the Fisher Exact test.

An interim analysis of 32 LMA and 32 ETT patients showed that two and three patients experienced postoperative vomiting episodes in each group, respectively. A Fisher Exact test showed no statistical difference between airway devices in the number of episodes of POV with a p-value of 1. This study will be continued, so that the sample size of 103 patients is reached for final evaluation.

ABSTRACT

Predictors of Outcome among Diabetics Receiving Below Knee Amputations

OMAR A. METWALLI   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Lillian S. Kao, MD, MS, Department of General Surgery

Supported by: The University of Texas at Houston Medical School and The Department of General Surgery, Lyndon B. Johnson County Hospital

Key Words: BKA, Diabetes, Guillotine

Background: Diabetes is the leading cause of non-traumatic lower extremity amputations. The goal of this study was to determine predictors of poor outcome (i.e. wound infection, systemic complications, death) in a population of medically underserved diabetic patients receiving below knee amputations.

Methods: A retrospective chart review of 156 diabetic patients, who underwent a below knee amputation over a period of 41 months (January 2007 to May 2010) at Lyndon B. Johnson County Hospital in Houston, TX, was performed. Variables, including BMI, comorbidities, initial presentation, pre-operative lab values and whether the patient received a single or two stage amputation, were included in the analysis. SPSS software was used to perform descriptive, univariate and multivariate regression analyses.

Results: Comorbidities found to positively correlate with post-operative complications included: history of ischemic heart disease (odds ratio [OR] 5.00, 95% confidence interval [CI] 1.44, 17.36, $P = 0.011$), history of pre-existing chronic kidney disease (CKD) (OR 3.18, 95% CI 1.04, 9.69, $P = 0.042$), and being a past smoker (OR 2.40, 95% CI 1.02, 5.68, $P = 0.045$). The preoperative lab values found to correlate post-operative complications were: PT (OR 1.50, 95% CI 1.12, 2.00, $P = 0.006$), INR (OR 6.17, 95% CI 1.45, 26.20, $P = 0.014$) and PTT (OR 1.09, 95% CI 1.01, 1.18, $P = 0.020$).

Conclusions: A history of ischemic heart disease, CKD, or being a former smoker, as well as elevated pre-operative PT, INR and/or PTT values are risk factors for developing complications in healing after receiving a BKA among diabetic patients.

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ABSTRACT

The Prevalence of Dry Eye with Computer Usage

LAURA A. NORRIS   *The University of Texas at Houston Medical School*   *Class of 2013*

The purpose of this cross-sectional study is to correlate hours using visual display terminals (VDTs) with dry eye symptoms in a medical student population. Computer Vision Syndrome (CVS) has become more significant following the trend of increasing dependence on VDTs. Longer exposures to VDTs are associated with increased ocular surface symptoms such as dry eyes, burning sensation, redness, grittiness, and contact lens problems. VDTs are linked with ocular symptoms because they have shown to decrease the normal blink rate by as much as 60%. Fewer blinks can lead to corneal desiccation by tear film evaporation and can reduce the amount of Meibomian gland lipid excretion forming a less stable tear film. An Ocular Surface Disease Index (OSDI) can reliably assess the perception of dry eye symptoms and distinguish between people with a normal ocular surface and those with ocular surface disease. Greater OSDI scores indicate increasing severity of dry eye disease. Since the medical student population is exposed to more hours at VDTs, they are an excellent cohort to survey for dry eye disease. The first and second year medical students were surveyed with an OSDI and supplemental questionnaire regarding ocular surface history, hours of VTD use, perception of dry eyes and demographics. The primary outcome variable of the OSDI score was regressed against VDT hours and a two-sample t-test was used to compare the differences in OSDI and VDT usage between the classes. The 2nd year class (N=119) compared to the 1st year class (N=145) had higher OSDI scores overall (p=0.0135) and scored greater in the vision-related function (p=0.0011) and ocular symptom (p=0.0094) subsets. Specifically, the 2nd year class had a 3.35 point increase in the OSDI compared to the 1st year class (p=0.0081). 34.45% of the 2nd year students and 24.83% of the 1st year students reported having dry eyes. Of the students within each class that felt they have dry eyes, 65-69% reported the dryness in the evening, which is linked to dysfunctional tear syndrome. The 2nd year class had greater total number of hours/day using a computer than the 1st year class (p<0.0001) and an average increase in 2.15 computer hours/day during the first year of school. However, greater hours using a computer did not correlate to an increase in OSDI scores. The VDT that associated with a higher OSDI was hours/week watching TV or playing video games; for each hour there is a 0.48 point increase on the OSDI (p=0.0218). These results indicate a significant increase in dry eye symptoms over the first year of medical school with several probable associations. Since the majority of the symptomatic students perceived dry eyes in the evening, this is suggestive of dysfunctional tear syndrome. We are in the process of conducting further research to correlate dry eye disease with abnormal lipid profiles.

ABSTRACT

Axonal Hyperexcitability Induced by Serotonin Application Enhances Behavioral Responses

PRIYANKA P. PAREKH   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Edgar. T. Walters, Ph.D., Department of Integrative Biology and Pharmacology
Supported by: National Institute of Neurological Disorders and Stroke 1 T35 NS064931-01

Previous experiments in the marine snail *Aplysia californica* have shown that intrinsic axonal hyperexcitability in nociceptive sensory neurons is elicited by application of 5-HT (serotonin) to the proximal nerve trunk (Weragoda and Walters 2007), as well as to peripheral nerve terminals (Billy and Walters 1989). The present study sought to correlate this hyperexcitability with enhancement of the tail withdrawal reflex, as a test of the hypothesis that 5-HT-induced pathways leading to persistent nociceptor hyperexcitability cause behavioral sensitization. A preparation was developed consisting of the two pedal-pleural ganglia, their respective tail-innervating p9 nerves, and the tail; then 5-HT solution was applied directly to the isolated proximal nerve trunk. Behavioral responses were tested by electrical stimulation of the same nerve segment. Enhanced tail withdrawal responses occurred 18-24 hours after 5-HT exposure (248% +/- 37% of the pre-treated baseline response, n=5), as compared to the sham-treated control (153% +/- 40%, n=4). A second preparation was developed in which 5-HT solution was transiently perfused directly into peripheral tail tissue; defensive sensitization was exhibited for at least 90 minutes after 5-HT exposure (1 μM 5-HT: 400% +/- 90% of pretreated baseline, n=5; 10 μM 5-HT: 360% +/- 158%, n = 4) in comparison to the sham-treated control (56% +/- 10%, n=2). These results demonstrate the behavioral potency of peripheral 5-HT, and suggest that 5-HT-induced intrinsic axonal hyperexcitability contributes to sustained behavioral sensitization in *Aplysia.* Similarities in peripheral sensitizing effects of 5-HT on nociceptors in *Aplysia* and mammals support the possibility that primitive, highly conserved sensitization mechanisms may contribute to chronic pain after injury in humans (Walters and Moroz 2009).

ABSTRACT

Alterations in Intestinal Smooth Muscle Cadherin Levels in Abdominal Trauma
A potential cause for the decreased in intestinal motility

NGOC PHAM   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Karen Uray, PhD, Department of Pediatric Surgery & Charles Cox, MD, Department of Pediatric Surgery

Supported by:

Key Words: Edema, intestinal smooth muscle, motility, cadherin

Interstitial edema is a common and deleterious problem under a variety of pathologic and traumatic circumstances, very often in trauma patients with abdominal injuries. It can lead to organ dysfunction and failure in several organ systems, including pulmonary, cerebral, intestinal, and especially myocardial systems.

In this study, our current attention is focused on examining the molecular mechanisms used by intestinal smooth muscle cells to sense and respond to increased cellular stretch induced by edema development. Specifically, we will focus on alterations in cadherins, cell-cell adhesion proteins, during edema development. Our overarching hypothesis is that intestinal edema causes a decrease in intestinal motility by altering the expression levels of different cadherin subtypes. Microarray data obtained from a rat model of intestinal edema (n=4) show that intestinal edema induced a 3-fold increase in cadherins-3 (CDH3) and cadherins-17 (CDH17), and a 2-fold increase in cadherins-16 (CDH16) mRNA levels compared to controls. This is further confirmed by quantitative real-time PCR experiments. Our qPCR data shows when normalizing against the control (sham surgery) rat, the 6-hr induced edema rat (n=6) has a 4-fold increased in CDH3 but a 4-fold decreased in CDH17 and CDH16. The 2-hr induced edema rat (n=4) has a 2-fold increased in CDH3 and a 2-fold decreased in CDH17, but the CHD16 expression level is too low to be detected by qPCR with 90% confidence. This observation show that the longer the edematous state (or intestinal trauma in real life) is present, the more severe changes the cells suffered (worst prognosis). Stretched human intestinal smooth muscle cells (n=6) show a 2 fold change in CDH3 expression level, but no detectable changes in CDH16 and CDH17. This demonstrates that different cadherin subtypes play a different role in the signaling pathways that affect gut motility between rat and human. More importantly, our Western Blotting study show that the phosphorylation level of myosin light chain (MLC) is decreased in edematous induced rat intestine. Therefore, we conclude that edema causes tissue swelling with increased interstitial spaces. This increased in stress felt at the cell-cell junctions is being compensated by increasing cadherin expression. Changes in cell-to-cell adhesion lead to an intracellular signaling that causes a decreased in phosphorylation of MLC, resulting in a decreased in motility.

Understanding the particular genes underlie a disease is the first step in trying to provide therapeutic benefits to the patients. From there, correct therapeutic treatment (such as drugs that aim cadherin in target organ) can be proposed to improve or even resume the organ's function, i.e. increase motility of intestine in this case. Furthermore, the same principles can be applied to other cases with similar problems. In example, drugs that target cadherin protein level in failing heart may improve the contractility of the heart, thus resuming its function.

ABSTRACT

Impact of a thawed plasma protocol on blood component utilization and outcomes in severely injured trauma patients.

ZAYDE A. RADWAN   *The University of Texas at Houston Medical School*   *Class of 2013*

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

Supported by: Center for Translational Injury Research

Key Words: Transfusion, resuscitation, plasma, emergency department

Background: Recent changes in trauma resuscitation strategies have focused on the earlier transfusion of plasma and platelets in the course of hemorrhagic shock. However, while saline solutions and universal donor (O-/O+) red blood cells are available in most emergency departments, plasma and platelets are traditionally kept in the Blood Bank. To expedite the delivery and transfusion of plasma in severely injured patients, Memorial Hermann Hospital (MHH) recently implemented a thawed plasma (TP) protocol. This protocol makes TP available to the Trauma Team for immediate transfusion. We hypothesized that having TP stored in the emergency department for immediate use would (1) reduce time to first plasma transfusion, (2) reduce number of blood component units transfused within the first 24 hours of arrival, and (3) reduce mortality rates. **Methods:** TP protocol was initiated 02/01/10. Following IRB approval we evaluated all trauma patients admitted to MHH six months prior to initiation of the protocol and six months after initiation. Data was abstracted from the MHH electronic medical record system. Patients were included in the study if they (1) were a major trauma activation, (2) were transported directly from the scene, and (3) received at least one unit of plasma in the first 24 hours. We excluded patients who (1) were less than 18 years of age, (2) had greater than five minutes of CPR, (3) were pregnant, (4) were prisoners, or (5) had >20% body surface area burns. Primary outcome was time to first unit of plasma transfusion. Secondary outcomes included 24-hour blood product utilization and 24-hour and 30-day mortality. Statistical analysis was performed using STATA 10.0. Univariate analysis was performed for demographics and study outcomes. A multivariate logistic regression model was developed to evaluate whether exposure to the TP protocol was associated with a reduction in mortality, controlling for injury severity and physiology on arrival. **Results:** 218 patients met study criteria (101 in the pre-TP population, 117 in the post-TP population). Demographics and injury severity were similar. Compared to the pre-TP group, the post-TP group had a reduction in time to first plasma transfusion (42 min vs. 87 min, p<0.001), and 24-hour red blood cell (11.9 vs. 16.0 units, p=0.02). 30-day mortality and hemorrhage related deaths were not significantly different between the groups (11.7% vs. 18.6%, p=0.175 and 12.5% vs. 28.5%, p=0.178, respectively). However, regression analysis demonstrated a 60% reduction in the odds of mortality (O.R. 0.37, p=0.03). In addition, patients in the post-TP group achieved higher plasma: red blood cell ratios at 24-hours (71% vs. 56%, p=0.03). **Conclusions:** Implementation of thawed plasma protocol expedites the transfusion of plasma to the severely injured patient. Such a protocol is also associated with a reduction in overall blood product use. Moreover, this protocol was associated with a 60% odds reduction in 30-day mortality when controlling for injury severity and physiology on arrival.

ABSTRACT

Pathogenesis of Diffusely Adherent *Escherichia Coli* Diarrhea (DAEC)

ALLISON L. RAMSEY   *The University of Texas at Houston Medical School*   *Class of 2013*

Diffusely adherent *Escherichia coli* (DAEC), a recently described cause of traveler's diarrhea (TD), possesses a characteristic diffuse binding pattern upon infection of intestinal epithelial cells. The purpose of this study was to determine if a correlation was present between the possession of DAEC plasmid-borne genes, *aap, daaC, aafC, afa/dr,* with standard PCR technique, and the release of IL-8, an inflammatory marker in diarrhea, using HCT-8 cells and the Enzyme Linked Immunosorbant Assay (ELISA). Thirty-nine DAEC strains were obtained from subjects with TD acquired in Central America and Asia. Statistical analysis was performed to compare the presence of each gene with the amount of IL-8 produced after infection. High levels of IL-8 were defined as those above the nonpathogenic HS control strain in pg/ml. Thirty-seven (95%) DAEC strains were found to have ≥1 virulence gene, of which *aap* was the most commonly found, occurring in 36 (92%). Twenty-eight (72%) DAEC strains produced moderate to high levels of IL-8. There was no obvious relationship between possession of virulence genes and production of IL-8. This study provides evidence that DAEC is a virulent strain when isolated from stools of persons with TD. Nearly all strains possessed well described virulence properties and most elicited an inflammatory response when exposed to epithelial cells. We believe that DAEC should be considered a potentially important cause of TD. Further study is indicated with other diarrheagenic *E. coli* to determine unique virulence features of DAEC strains.

ABSTRACT

Expression of channelrhodopsin-2 in the visual cortex of non-human primates

PAUL J. RONCAL   *The University of Texas at Houston Medical School*   *Class of 2013*

Optogenetics, the manipulation of neuronal gene expression for the ability to control neuronal activity with light, is a new field of study that has the potential of improving the spatial and temporal control of action potentials and advance clinical neuromodulation. Of special interest is Channelrhodopsin-2 (ChR2), a photosensitive cation channel that can control membrane potentials and may be expressed in specific neurons through the use of lentiviruses. Being able to perturb precisely specific cell types and pathways in the visual cortex of non-human primates would elucidate possible neuronal network mechanisms in the human brain that can lead to novel therapies. A lentivirus construct was injected at two sites in the V4 area of the visual cortex of a *Macaca mulatta* (Rhesus Macaque) to induce the expression of Channelrhodopsin-2 selectively to excitatory neurons. We began recording local field potentials (LFP) after 14 days of the injection with a 16 channel U-probe and used an optical cable to send pulses of blue wavelength (473 nm.) After observing the LFP's, our results were inconclusive possibly due to one of the following factors: injection depth had few excitatory neurons, shift of brain matter, or failure of virus expression. Further injections will address these shortcomings.

ABSTRACT

Urinary biomarkers that detect, categorizes, and may differentiate renal injury due to chemical exposures.

REEM SABOUNI   *The University of Texas at Houston Medical School*   *Class of 2013*

This project seeks to validate a specific panel of urinary biomarkers in humans that detects, categorizes, and may differentiate renal injury due to chemical exposures like those resulting from occupational exposures of petrochemical workers (long-term, repeated exposures, low dose) from other causes of kidney injury. The panel may help differentiate toxic exposure induced renal injury from chronic renal injury related to hypertension and diabetes and other common chronic diseases. These biomarkers might be used to decrease adverse occupational-exposures and subsequent renal injury. We will ultimately recruit a study group consisting of 80-100 people working in the petrochemical industry and two control group consisting of 50 first-degree family members that do not work in the petrochemical industry and 50-70 residents of the same neighborhoods as the study group that are gender and age matched. From each participant, urine will be collected twice in a two-day span, once before work and once after work, along with a blood sample taken only once before work. The samples will then be run through various assays using specific biomarkers and tests that should allow for the identification of individuals with CKD and may identify more precisely nephron site-specific renal injury. The site specificity is accomplished by detection of particular enzymes and proteins by certain parts of the nephron during toxin induced damage. My contribution to the study is during phase one that will be dedicated to a cross-sectional evaluation of exposure and urine biomarkers. I have helped recruit the test subjects and collect samples, have created/administered a survey instrument to track work experience/possible exposures and comorbid medical conditions, and have performed the various biomarker assays included in the panel including ELISAs for urinary proteins and enzyme linked colormetric assays. Data is still in the process of being collected and analyzed.

ABSTRACT

Autologous Platelet Rich Plasma (aPRP) Impact on Clinical Outcome in Ascending Aortic Surgery with Deep Hypothermia Circuit Arrest

DEAN L. SAGUN   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Shao Feng Zhou, MD, Department of Cardiovascular Anesthesiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases 5 T35 DK007676-18

Key Words: Autologous Platelet Rich Plasma (aPRP), Ascending Aorta, Blood Transfusion

Ascending aortic surgery with deep hypothermic circulatory arrest (DHCA) often requires massive blood transfusions to correct platelet and coagulation factor deficits. Traditional therapy mainly depends on blood and blood product transfusion, such as red blood cells (RBC's), fresh frozen plasma (FFP), platelets, and cryoprecipitate, combined with blood conservation techniques (cell saver and pharmacologic agents). It has been suggested that the use of autologous platelet rich plasma (aPRP) may be an effective, safe and simple process to preserve the patient's own platelets and coagulation factors. This study was designed to investigate the effectiveness of aPRP on the requirement for blood transfusion and clinical outcomes in ascending aorta and arch repairs with deep hypothermia circuit arrest (DHCA). We retrospectively reviewed 649 cases of ascending aorta repairs with DHCA, ages 18-80 performed between 2003-2009. Patients were divided into 2 groups: Group aPRP (n= 274) and Group control (375). Data (transfusion, complications) were analyzed using mean (±SD) and frequency distribution. Two-sample t-test or Chi-Square test was used. A p-value of < 0.05 was considered significant. Demographics, surgical characteristics, pre- and post-operative homeostatic, hematocrit values as well as renal function between two groups were similar. Intra-and post-operative blood transfusions were significantly reduced in aPRP group. In addition, the use of aPRP transfusion was associated with a reduction in most complications (stroke, myocardial infarction, hemodialysis). More importantly, mortality was reduced by the use of aPRP (Table 1). In conclusion, use of aPRP in ascending aorta and arch repairs with DHCA surgery reduces morbidity and mortality associated with DHCA.

TRANSFUSION / COMPLICATIONS	Non-aPRP Group N=375 (±SD)	aPRP Group N=274) (±SD)	p-value
PRBC (units)	5.00±4.14	2.30±2.30	<0.001
FFP (units)	5.73±4.82	2.09±3.24	<0.001
Platelets (units)	10.16±5.96	2.68±4.51	<0.001
Stroke (cases)	25 (6.67%)	5 (1.82%)	0.0069
Myocardial Infarction (cases)	6 (1.60%)	0 (%)	0.0433
Hemodialysis (cases)	41 (10.93%)	13 (4.74%)	0.093
Mortality (cases)	32 (8.53%)	13 (4.74%)	0.0864

ABSTRACT

The Effect of Weight Loss on Psoriasis Area Severity Index and Serum TNF- α Levels in Obese Adults with Psoriasis

BRITTANY L. SAMBRANO   *The University of Texas at Houston Medical School*   *Class of 2013*

Psoriasis is a systemic inflammatory disease that affects 3% of the population worldwide and causes significant physical and psychological distress. Plaque psoriasis, a helper T-cell (Th1) mediated disease, occurs in response to the upregulation of IFN-γ, TNF-α, and various interleukins. Overproduction of these inflammatory cytokines leads to cutaneous plaque formation characteristic of the disease. Cytokine mediated inflammation, present in both psoriasis and obesity, raises the risk of developing myocardial infarction and the metabolic syndrome. Although psoriatic patients have an increased risk of myocardial infarction as a direct result of elevated TNF-α levels, the impact of weight loss in psoriasis patients on TNF-α levels is currently unknown.

A clinical trial was designed to evaluate the effect of weight loss on the severity of psoriasis and how TNF-α levels correlate with that weight loss in adult patients. A total of fifty male and female participants with moderate to severe plaque psoriasis and a Body Mass Index (BMI) ≥ 30 are to be enrolled in a 6 month program of weight loss counseling. Baseline evaluation will include assessment of BMI, measurement of serum TNF-α, and evaluation of psoriasis using the Psoriasis Area Severity Index (PASI), a validated measure that assesses redness, thickness, scaliness, and affected body surface areas. Participants will enroll in a certified nutritionist guided weight loss program to include individual nutritional and physical activity counseling. Psoriasis severity will be reevaluated at Day 0, Month 3, and Month 6; TNF-α levels will be measured at Day 0 and Month 6. Primary outcome measures will determine the mean change in PASI score from baseline to 6 months. Secondary outcome measures will assess the amount of weight loss achieved, change in serum TNF-α levels, and the subject's assessment of overall improvement of psoriasis.

ABSTRACT

Infarct resolution as a target for ischemic stroke treatment with anti-diabetic medication: the role of CD36 scavenger receptor

KELLAN M. SCHALLERT   *The University of Texas at Houston Medical School*   *Class of 2013*

The CD36 scavenger receptor gene is regulated by the transcription factor peroxisome proliferator activated receptor-γ (PPAR-γ). Previous studies show that activation of PPARγ by rosiglitazone (Rosig), a thiazolidinedione class PPARγ agonist and anti-diabetic medication, can induce CD36 expression in microglia. This upregulation ultimately leads to more efficient phagocytosis-mediated clearance of brain hematoma as well as improved functional recovery after hemorrhagic stroke in mice. The present study was designed to determine whether CD36 also contributes to enhanced clearance of infarcted tissue after ischemic stroke and whether this manipulation improves neurological recovery. Mice, wild type (WT) and CD36-null, were subjected to unilateral 60-minute middle cerebral artery occlusions (MCAo), a model of ischemic stroke. They were treated with 0.1mg/kg intraperitoneal Rosig or vehicle 30 minutes after MCAo and daily for five consecutive days. Neurological deficit scores (NDS) were determined using standard behavioral tests on Days 1, 2 and 5. The infarct volume and the expression of PPARγ-regulated genes in the stroke-affected hemisphere on Day 5 were evaluated using immunohistochemistry and real-time PCR.

After MCAo, normal WT mice displayed improved neurological function (23% reduction of NDS; $p < 0.05$) between 2 and 5 days. However, CD36-null mice showed no significant recovery. At all time points, WT animals receiving Rosig showed less behavioral impairment than WT animals receiving vehicle. Rosig did not benefit CD36-null mice after stroke. Histological analysis of brain tissue stained for CD36 confirmed an increase in CD36 protein in the peri-infarcted area for Rosig treated WT mice compared to the vehicle-treated group. PCR analyses confirmed the effectiveness of Rosig in enhancing mRNA expression of the CD36 gene.

The superior behavioral recovery in WT mice, especially those treated with Rosig, combined with the lack of improvement in CD36-null mice, suggests the importance of CD36 protein in the process of functional recovery after cerebral ischemia. The Rosig induced recovery occurred at least 2 days after the onset of stroke supporting the hypothesis that CD36 is beneficial through regulation of a delayed infarct clearance process involving microglia/macrophages as opposed to acute neuroprotection. Further analyses are required to determine the specific morphological and biochemical changes in the WT and CD36-null mice.

ABSTRACT

Examination of the Eradication of Existing *Staphylococcus aureus* Biofilms by Exposure to Silver Nanodressing in an *In Vitro* Infection Model

JAMES C SHAW   *The University of Texas at Houston Medical School*   *Class of* 2013

Sponsored by: Catherine G. Ambrose, Ph.D. Department of Orthopaedic Surgery

Supported by: Department of Orthopaedic Surgery, The University of Texas at Houston Medical School

Key Words: Biofilm, silver nanodressing, *Staphylococcus aureus*, osteoblast

Bacterial infections are a common complication for patients with open wounds such as diabetic foot ulcers, burn injuries, or some traumatic injuries. *Staphylococcus aureus* is responsible for most of these wound infections. As a survival mechanism, *S. aureus* organizes into surface-associated aggregates within an extracellular matrix, termed a biofilm. Biofilm bacteria possess an increased resistance to antimicrobials and host defenses, which can cause wounds to become chronically infected and possibly life threatening. Due to the antimicrobial properties of silver, it has been used to prevent biofilm growth. Here, we tested the ability of silver to eradicate existing biofilms, which has never been tested. Using an *in vitro* model developed previously in our lab to mimic an open wound with exposed bone, *S. aureus* biofilms were grown statically at 37°C in 24 well-plates on polymethylmethacrylate (PMMA) bone cement discs in synthetic interstitial fluid (SIF), consisting of physiological concentrations of salts, glucose, hyaluronic acid and fetal bovine serum. Day four biofilms were exposed to six different amounts (2 – 11 mg in 0.5 ml SIF) of Acticoat® 3 (Smith and Nephew), a silver nanodressing. After 24 hrs the biofilms were stained with cell viability dyes and imaged using a confocal laser-scanning microscope. The images were analyzed using software previously developed in our lab. The results show that any exposure to the dressing decreased the total biofilm biovolume (both live and dead cells) to about 8% of the unexposed cells. Furthermore, with increasing amounts of nanodressing the ratio of dead cells to live cells increased from 1/4 to nearly 1. Currently, the effect of the silver nanodressing on growing osteoblasts and *S. aureus* planktonic cell is being evaluated. It is desired to find a "safe" amount of nanodressing that will eradicate bacterial biofilms while preserving human cells such as osteoblasts.

ABSTRACT

Novel Use of DyLight™ Fluorescent Label to Visualize Collection of Monoclonal Antibody in a GBS Sciatic Nerve Crush Murine Model

JASON T. SHURB   *The University of Texas at Houston Medical School*   *Class of 2014*

Sponsored by: Kazim A. Sheikh, MD, Department of Neurology

After the near eradication of polio, Guillain-Barré syndrome (GBS), also referred to as acute inflammatory demyelinating polyneuropathy (AIDP), has become the most common cause of acute flaccid paralysis worldwide. Autoantibodies directed against cell surface glycans carried by gangliosides, which are sialic acid-containing glycosphingolipids enriched in peripheral nerve fibers, have become the main focus of research in GBS. Over the last 15-20 years several lines of evidence have linked IgG autoantibodies directed against GD1a to the pathogenesis of GBS particularly to axonal forms of disease.

In this particular investigation the GD1a-E6 mAb were produced using the hollow fiber bioreactor facility at Johns Hopkins University. Verification that the antibodies were active against the peripheral nerve GD1a gangliosides was performed using ELISA. 3 mg of the GD1a-E6 mAb was then conjugated to Pierce DyLight™ 549 Amine Reactive Fluorescent Dye. Sciatic nerve crushes were performed on 2 CL57BL/6 male mice. 72 hours post-surgery the mice were injected with 1 mg of the conjugated mAb. The mice were sacrificed 48 hours post-injection of the injection. The animals were perfused and their sciatic nerves were extracted and viewed under an epifluorescent microscope which showed profound accumulation at the crush site and progressive accumulation from the proximal to the distal end of the nerve as would be expected. This novel experiment of using labeled antibodies in-vivo can be used in numerous future experiments where knowing the location of antibody accumulation is critical.

ABSTRACT

Body Mass Index (BMI) as a Predisposing Factor for Aortic Dissection

SELINA M. SINGH　　　*The University of Texas at Houston Medical School*　*Class of 2013*

Sponsored by:　Anthony L. Estrera, MD, Department of Cardiothoracic and Vascular Surgery
Supported by:　*The University of Texas at Houston Medical School*
Key Words:　　Aortic dissection, BMI

Aortic dissection is a potentially life-threatening emergency in which the media layer of the aortic wall degenerates causing bleeding within and along the aortic wall. Acute aortic dissection remains the most common aortic catastrophe with 6,000 to 10,000 cases annually in the United States. The etiology of aortic dissection is unknown, but several factors including arterial hypertension, stress, and genetics likely play a role. The purpose of this study was to determine if there is an association between body mass index (BMI) and aortic dissection. A retrospective chart review of 481 patients presenting with aortic dissection from 2003 to 2009 was performed. Each dissection was classified according to the Stanford method (Type A or Type B) and as acute or chronic. BMI was calculated and sorted into standard weight status categories based on CDC guidelines. Our results indicate that 34% of dissection patients were obese and 40% were classified as overweight. According to the National Health and Nutritional Examination Survey, 34% of U.S. adults aged 20 and over are obese and 34% are overweight. Subgroup analysis based on the type of dissection revealed nearly identical results: 35% and 40% of Type A dissections and 33% and 40% of Type B dissections were obese and overweight, respectively. We expected a greater percentage of patients with aortic dissection to fall into these categories. Aortic dissection has a multi-variable etiology and our current understanding is limited to the roles of hypertension, age, and connective tissue disorders. Determining that BMI is not associated with dissection contributes to our understanding of the predisposing factors for aortic dissection.

ABSTRACT

Comparison of Biofilm Formation on Different Biomaterials in an *in vitro* Diabetic Joint Model

BRIAN D. STOVER   *The University of Texas at Houston Medical School*   *Class of 2013*

Biofilm formation on in-dwelling devices constitutes the most common cause of nosocomial infections in the United States and can be attributed as the main cause of chronic infections. Diabetics are particularly susceptible to these infections due to compromised vascularity in their extremities and a weakened immune response. We have adapted an *in vitro* biofilm model previously developed in our lab to evaluate biofilm growth on different orthopaedic biomaterials. Polymethylmethacrylate (PMMA) bone cement, steel, TNZF alloy, and Grade 2 and 5 anodized and non-anodized titanium alloy discs were used as growth substrates for *Staphylococcus aureus* and *Enterococcus faecalis*, which are two of the most common etiological agents of orthopaedic biofilm infections. Each pathogen and disc combination was incubated statically in 24-well plates at 37°C in a synthetic interstitial fluid, which was exchanged daily. On days 1 – 7, two discs of each combination were stained with cell viability dyes and imaged using a confocal laser scanning microscope. Grade 5 titanium alloy supported the most *S. aureus* biofilm growth, whereas blue anodized Grade 2 titanium and steel supported the least growth. However, during days 1 and 2 there was significantly less growth on all the titanium discs compared with PMMA, steel, and TNZF alloy. These results suggest that titanium implants may inhibit *S. aureus* biofilm growth long enough for either the immune response or antimicrobials to prevent infection. The results were more varied for *E. faecalis*, although titanium discs supported the most biofilm growth and TNZF alloy the least.

ABSTRACT

Development of A Molecular Cloning Protocol to Verify the Results of 16S rDNA-Denaturing Gradient Gel Electrophoresis (DGGE) Analysis in the Identification of Bacteria in Diabetic Infections

TIFFNEY R. TEZINO   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Catherine Ambrose, PhD, Department of Orthopaedic Surgery
                          Heidi B. Kaplan, PhD, Department of Microbiology and Molecular Genetics

Over 20 million children and adults are living with diabetes in the United States and infections are often more severe in diabetics compared to non-diabetics due to a myriad of complications associated with the disease. Many of the infections are polymicrobial and it has been shown that conventional culture techniques are not adequate to identify these microbes. An alternate method, 16S rDNA PCR amplification combined with denaturing gradient gel electrophoresis (DGGE) has had some success in differentiating pathogenic bacteria in tissue samples for subsequent DNA analysis and identification. However, in a pilot study, 16S rDNA PCR/DGGE did not identify all the bacteria that culture analysis did, and thus an alternative molecular technique to determine the sensitivity and specificity of 16S rDNA PCR/DGGE is indicated. The purpose of the experiment was to develop an appropriate experimental design for cloning bacterial 16S rDNA sequences . During this experiment, two different cloning protocols were employed to determine the one that would be most effective for cloning the 16S rDNA. One involved using the TOPO TA Cloning Kit (Invitrogen) and the other was a more standard cloning strategy using restriction endonucleases. Neither of the cloning strategies yielded any usable results. The trouble-shooting steps eliminated some of the possible causes of the failed cloning attempts but ultimately were not successful in identifying the actual cause.

ABSTRACT

BMP Regulates Autophagy in Acute Pancreatitis (AP)

MATTHEW TYLER   *The University of Texas at Houston Medical School*   *Class of 2013*

Sponsored by: Tien Ko, M.D., Department of Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases 5 T35 DK007676-18

Key Words: Autophagy, C57BL

Introduction: Autophagy is a homeostatic mechanism in which a cell 'recycles' cellular material in response to dynamic changes in its energy pools. Recently, it has been shown that dysregulated autophagy contributes to AP. Autophagy is controlled by sequential expression of proteins such Beclin-1 and LC3-II. Beclin-1 is expressed during phagophore formation which precedes LC3-II expression during autophagosome formation. Previously, we have shown that BMP signaling is activated in cerulein (CR)-induced AP, and treatment with noggin, a BMP antagonist, attenuates CR-induced AP (Yang W et al. APA Annual meeting 2009). The purpose of this study is to test the hypothesis that BMP regulates authophagy in CR-induced AP. Methods: C57BL/6 mice were randomized into two groups (n=7/group): (1) 9 hourly injections of CR (50 µg/kg, ip); (2) pretreatment with noggin, (0.5 µg/kg, ip) followed by CR (50 µg/kg, 9 hourly ip injections). Mice were euthanized 1 hr after last CR injection. Pancreas tissue was harvested to examine for the presence of autophagic vacuolization by electron microscopy and for autophagy markers by immunoblotting. Results: Noggin pretreatment attenuated CR-induced autophagic vacuolization, and lowered LC3-II levels by 72.5% compared to CR treatment alone ($p < 0.05$). Interestingly, in the presence of noggin, CR resulted in a 2.5-fold increase in Beclin-1 levels compared to CR treatment alone ($p < 0.05$). Furthermore, noggin pretreatment restored expression of the autolysosome (late autophagy) markers, Rab7 and LAMP2. Conclusion and Discussion: These results suggest that noggin restores autophagic 'flux' at the transition from phagophore to autophagosome which is associated with attenuated AP. Targeting BMP signaling pathway may be a novel strategy to block dysregulated autophagy seen in AP.

ABSTRACT

TGF-β Inhibits BMP Signaling in Pancreatic Stellate Cells to Promote Pancreatic Fibrosis

MINI G VARUGHESE   *The University of Texas at Houston Medical School*   *Class of 2013*

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

Background: Acute pancreatitis (AP) is a necrotizing inflammatory condition. Recurrent episodes of AP (RAP) lead to chronic pancreatitis (CP), which is characterized by inflammation, fibrosis and loss of exocrine and endocrine functions. Pancreatic stellate cells (PSCs) are the key effectors in pancreatic fibrosis and have become the focus of the mechanistic study in recent years. Transforming growth factor (TGF)-β is a potent activator of PSCs. Activated PSCs express α-smooth muscle actin (α-SMA) and produce copious amounts of extracellular matrix (ECM) proteins. Although bone morphogenetic proteins (BMPs) are known to antagonize TGF-β's fibrogenic effects in multiple organs, the role of BMPs in pancreatic fibrosis is not known. Previously, we have shown that BMP2 inhibited TGF-β-induced PSC activation and ECM expression and that TGF-β induced gremlin, a BMP antagonist, in primary PSCs. The pancreas from the RAP mouse model revealed significant fibrosis. This particular study sought to examine the expression pattern of gremlin and fibrosis markers in PSCs isolated from the RAP mouse model. **Methods**: Female Swiss Webster mice (8-10 weeks old) were randomized into two groups (n=4/group): RAP was induced by a secretagogue cerulein (50 µg/kg/0.1 ml, ip, 5 hourly injections/day, 3 days/week, for 8 weeks). Normal saline control was given the same volume and frequency. The mice were euthanized and the pancreas was harvested on day 4 after the last injection. Pancreas was pooled from 4 mice for each group and PSCs were isolated using outgrowth method. Immunofluorescence analysis was done on intact cells for α-SMA, vimentin, fibronectin and gremlin. IF intensities from 3 different imaging fields were measured using ImageJ software. **Results**: Pancreas from RAP mice generated higher numbers of PSCs with stronger staining of α-SMA, fibronectin, vimentin and gremlin compared to PSCs from control mice. However statistical significance was not reached since only limited number of fields (n=3) were analyzed for IF (t-test, p>0.05). **Conclusions:** Previously we have shown that BMP2 inhibited fibrogenic effect of TGF-β in PSC activation and ECM expression, and TGF-β induced gremlin expression in PSCs in vitro. The high gremlin expression in activated PSCs isolated from RAP mice in this study further supports our hypothesis that gremlin induction composes a novel mechanism via which TGF-β down-regulates BMP signaling to promote pancreatic fibrosis.

Identification of Rickettsial Effector Proteins by *Agrobacterium*-mediated Type IV Secretion

ELISE A. WALKER   *The University of Texas at Houston Medical School*   *2013*

Sponsored by: Peter J. Christie, PhD Microbiology
Supported by: Peter J. Christie, Ph.D.
Key Words: T4SS, VirD4, *Agrobacterium tumefaciens, Rickettsia rickettsi*

Anaplasma phagocyophilum and Rickettsia rickettsi are the causative agents of two tick-born illnesses which are important emerging infectious diseases; Human granulocytic anaplasmosis and Rocky Mountain spotted fever. Given their obligate intracellular lifestyles, it is difficult to characterize the pathogenic mechanisms associated with these bacteria. Both organisms contain Type IV secretion systems (T4SS), present in several clinically relevant organisms which enable the delivery of effector proteins to promote survival, colonization, and spread of disease. These T4SS share homologous proteins with the well-characterized T4SS of Agrobacterium tumefaciens, most notably the substrate coupling protein VirD4 and channel subunit proteins VirB1-VirB11. The relatedness of these three organisms and the homology among their proteins facilitated our development of a surrogate infection model which will allow for the identification of Rickettsial family-effector proteins that are delivered through the T4SS during infection. In this study, we engineered A. tumefaciens strains to produce a chimeric T4SS composed of Agrobacterium VirB channel subunits coupled with the VirD4 substrate receptor from each of the two Rickettsial family members. These strains will be tested for their capacity to transfer DNA and protein substrates into target cells as well as mobilizationof IncQ plasmid to agrobacterial recipient cells.   Next, we constructed a plasmid containing a PVirB-Flag segment with downstream restriction sites. Fragmented Rickettsial genomic DNA placed downstream of PVirB-Flag will be introduced into a leaky A. tumefaciens secretion channel strain. The resulting strains will be used to screen for gene fragments whose products mediate protein transfer by monitoring for extracellular Flag release. Candidate effector proteins identified through these screens will be characterized in future studies for their potential to function in Rickettsial infections.

ABSTRACT

Metabolic Signals as Regulators of Cardiac Growth in Diabetes

NATHAN R. WEBB   *The University of Texas at Houston Medical School*   *Class of 2013*

Background: The metabolic stress of diabetes results in extensive remodeling of the heart, including myocyte hypertrophy. The mTOR signaling pathway has long been implicated in cardiac hypertrophy. This pathway is upregulated in the diabetic rat heart for reasons still unknown. The purpose of my project was to examine whether impaired glucose oxidation and accumulation of intermediary metabolites in the hearts of diabetic rats modulate mTOR signaling and cardiac growth. **Methods:** Hearts from 8 week old male Zucker Diabetic Fatty (ZDF) and Zucker Lean (ZL) rats were perfused *ex vivo* using the isolated working heart preparation. The perfusate contained physiological concentrations of glucose (5 mM), oleate (0.4 mM), and insulin (40 µU/mL). Cardiac power and rates of substrate oxidation were measured every five minutes. At the end of each perfusion, activation of proteins in the insulin signaling cascade was examined, and glucose 6-phosphate levels were measured in frozen tissue extracts. **Results:** Cardiac power was significantly diminished in diabetic hearts. Rates of glucose oxidation were also suppressed, while rates of oleate oxidation were unchanged. Intracellular glucose 6-phosphate levels were 2.5 times higher in ZDF than in ZL rats. Akt, a nodal point in the insulin signaling pathway which lies upstream of mTOR, showed a greater than three-fold *decrease* in phosphorylation in diabetic hearts compared to controls. In contrast, phosphorylation of mTOR and its downstream target p70S6K was significantly *increased* in diabetic hearts. **Conclusions:** The accumulation of glucose 6-phosphate activates the mTOR signaling pathway in spite of a downregulation of the insulin signaling pathway. The data support the novel hypothesis that intermediary metabolites act as signaling molecules regulating pathways of cardiac growth.

ABSTRACT

Thromboelastography (TEG) in Acute Ischemic Stroke

JEREMY S. WETZEL   *The University of Texas at Houston Medical School*   *Class of 2013*

Background: TEG demonstrates the dynamics of coagulation (see figure 1). R=time to clot initiation; K=speed of clot buildup; Delta=time to maximum rate of thrombus generation (intensity of thrombin burst); G=clot strength (increased in platelet-rich clots). There are limited data available about TEG and its utility in acute ischemic stroke (AIS). We studied TEG in patients with AIS to: 1. compare baseline TEG values in AIS vs controls; 2. distinguish clot subtype; 3. determine extent of fibrinolysis after tPA bolus.

Methods: Consecutive patients with AIS who presented within 3 hours of onset were included. Venous blood was drawn upon arrival to the ED and 10 minutes after initiation of tPA.

Results: A total of 32 AIS stroke patients and 46 controls were evaluated; 15/32 AIS patients had both pre- and post-tPA TEG. Mean age was 67±18 years, 50% were female; of 32, 14 were of cardioembolic etiology, 3 were large artery atherosclerotic, 4 due to small artery occlusion, and 11 other or unknown. Baseline R was 5.8 minutes shorter ($p<.0001$) and K was 1 minute shorter ($p<.0001$) in AIS patients compared to controls after correcting for age. Delta averaged 0.6 ± 0.6 minutes (vs 0.7-1.1 minutes in controls). All these findings indicate hypercoagulability in AIS. Nineteen AIS patients had elevated G values indicating platelet–rich clots (G = 11.3 ± 2.3 Kd/cm2) while the remaining patients had lower G values (G = 7.9 ±0.6 Kd/cm2) ($p<.001$) which, along with lower delta, indicates "red" clot with more thrombin contribution and less platelets (see figure 2). G significantly decreased post-tPA compared to baseline ($p<.0001$) confirming the fibrinolytic effect of tPA.

Conclusion: AIS patients are hypercoagulable due to robust thrombin generation, and form clots with varying strength and composition, which undergo fibrinolysis by tPA. TEG may provide a way to monitor and adjust thrombolytic therapy so that it is safer and more effective, as well as individualized to the patient.
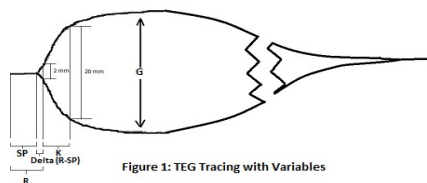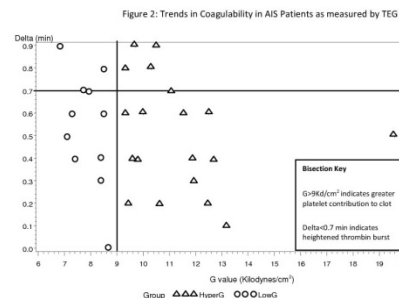

Figure 1: TEG Tracing with Variables

Figure 2: Trends in Coagulability in AIS Patients as measured by TEG

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ABSTRACT

Establishing the relationship between drug sensitivity and the epithelial-to-mesenchymal transition in non-papillary urothelial carcinoma

S. Alex Woods   *The University of Texas at Houston Medical School*   *Class of 2013*

Urothelial carcinoma (UC) occurs in two distinct forms: papillary and non-papillary. Non-papillary UC is the more lethal form due to its tendency to invade the bladder muscle, metastasize, and most importantly, be resistant to therapeutics (approximately 50% of tumors have low sensitivity to therapeutics). Presently, modern medicine is unable to distinguish between the drug-sensitive and drug-resistant subsets of non-papillary UC, and still more, treatment options for drug-resistant UC are limited and have poor outcomes. Based upon recent literature and observing that non-papillary UC cell lines have different expression profiles of epithelial and mesenchymal phenotypic markers, we hypothesize that resistance to therapeutics may be conferred upon cells as a consequence of the epithelial-to-mesenchymal transition (EMT). If true, EMT-marker expression analysis of tumor specimens from patients may provide a clinical resource for diagnosis and treatment of UC, and furthermore, it may offer insight into the development of new therapeutics for drug-resistant non-papillary UC. To test our hypothesis, we treated urothelial carcinoma cell lines UC-1, UC-14, and BV with the drugs cisplatin and gemcitabine at different concentrations and combinations and observed their effects on cellular apoptosis by PI-FACS analysis and PARP Western blotting. We found that within these three cell lines, our hypothesis was confirmed: sensitivity to therapeutics decreased with increased expression of mesenchymal markers and decreased expression of epithelial markers. However, observing the gamut of 18 non-papillary urothelial carcinoma cell lines, we found that the contrary was true: sensitivity to cisplatin and gemcitabine increases with increased mesenchymal markers and decreased epithelial markers. Given these findings, it appears that the EMT alone does not regulate drug sensitivity and that there are other mechanisms involved, namely DNA repair by homologous recombination.

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Undergraduate Students

ABSTRACT

Glyoprotein Ib-IX complex bonding to von Willebrand factor

JEFF K. ABBOTT   *University Of Oklahoma*   *Class of 2012*

The glycoprotein Ib-IX complex plays a crucial role in the initiation of platelet activation after binding to von Willebrand factor, as well as hemostasis. Many other functions of this complex have been found, however, the structure and organization of this glycoprotein complex has yet to be determined. It has been proven that the complex is made up of 4 subunits of 3 types: 2 Ibß subunits, 1 Ibα subunit, and 1 IX subunit. To better understand the form of this protein complex, a crystallized protein model is to be formed. In order to better understand the structure to help accomplish this model, we used limited proteolysis to assess the rigidity and flexibility of the subunits and where the polypeptides are cleaved. The subunit of concentration for this abstract is the Ibß subunit. The subunit was located and isolated through sodium dodecyl sulfate polyacrylamide and 2 dimensional gel electrophoresis. Then Ibß was then put into a Western blot along with N-terminal and C-terminal antibodies along with trypsin to cleave the subunits. The presence of the N-terminal antibodies bound to the N-terminus in the presence of trypsin indicates that at least, some of the subunit has not been cleaved. On the other hand, there was no presence at all of the C-terminus bound to its antibody. This illustrates that when cleaved, the subunit is cleaved on the cytoplasmic, C-terminal interior of the cell. These results explain where the subunit is most flexible and will later help determine the best way to determine the crystal structure of the entire GP Ib-IX structure.

ABSTRACT

Facial Expression Analysis Using 6D Data: Application to Autism

CAREN P. ABRAHAM *Rice University* *Class of 2012*

Sponsored by: Katherine A. Loveland, PhD, Department of Psychiatry and Behavioral Science

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Facial expression analysis, autism, computational methods

Autism spectrum disorders can be characterized by abnormalities in social and emotional behavior, including unusual facial expressions. Social/emotional functioning consists of two components: observation and interpretation of the surrounding environment, including comprehension of verbal and nonverbal communication, and expression of social-emotional behavior, through both verbal and nonverbal means. The comprehension of nonverbal behaviors in people with autism has been extensively studied. However, little work has been done on the expression of nonverbal communication, specifically facial expression. This is likely due to the fact that current methods for coding and analyzing facial expressions are extremely long, expensive, and labor intensive. Currently, the analysis of facial expression requires the use of expert coders using the Facial Action Coding System (FACS) (Ekman and Friesen, 1978). FACS is a system used to divide the face into 64 different facial Action Units (AU) which allow various points on the face to be traced as the muscles of the face move to create an expression. Coders must be highly trained and able to discriminate fine facial movements with great precision. This process makes the study of facial expression very difficult. The goal of this project is to develop a computerized system for the analysis of spontaneously produced (i.e., real, not posed) dynamic facial expressions using 6 dimensional imaging data in a much faster and cost–efficient manner. 6D data is merely the image of a 2D face combined with its 3D geometry captured over the sixth dimension of time. This 6D system is already used to capture facial data for facial recognition purposes, however no algorithm is available for facial expression analysis of this data by a computerized system. In order to develop such a system, video stimuli were developed to elicit various spontaneous facial expressions (happiness, sadness, fear, disgust, surprise, and anger) from the test subjects. Twenty healthy adolescents and adults are being videotaped currently, and twenty more adolescents and adults with autism will be videotaped while they view these stimuli. The subjects' response videos will be analyzed by expert coders using FACS as well as the current version of the system for analyzing facial expressions. The two analyses will then be compared to validate and refine the computer analysis system. Comparison of the results from expert human coders to the results from the first version of the computerized system will be used to develop a more accurate analysis algorithm that can be used, hopefully, for further research on how people with autism express emotion as well as how autism develops in children.

ABSTRACT

NSD Family: Highlights of NSD1

LAURA E. BARBRE   *Louisiana State University*   *Class of 2011*

Sponsored by: Phillip Carpenter, M.D.
Supported by: University of Texas Medical School-Houston Summer Research Program
Key Words: NSD1, Mes-4

NSD1, nuclear receptor binding set domain protein, is one of three members of the "NSD family". The genes encoding these proteins are complex, containing multiple domains. The SET domain, which modifies histones via methylation, is a component of all members of the NSD family. Mutations in *NSD1* are associated with developmental disorders such as Sotos Syndrome, which is an overgrowth disease characterized by cerebral gigantism and learning disabilities. Approximately five percent of patients with Acute Myeloid Leukemia possess translocations between *NSD1* and *Nup98*. NSD1 has also been implicated to be involved in estrogen and androgen signaling pathways indicating that it could be important in breast and prostate cancer. In *Mus musculus*, an NSD1 knock out is embryonic lethal, indicating that murine *NSD1* is an essential gene. The *Drosophila melanogaster* ortholog of the human *NSD1* gene is *Mes-4*. In flies, this gene is the only member of the NSD family and it methylates histone H3-K36 in a manner similar to that of NSD1. My primary task in the lab was to detect the exact place of a suspected *Mes-4* deletion in a fly called ED6280. Upon attaining the ED6280 fly I found the junctions of the deleted region by PCR. Because the deletion was made with a transposable P-element, I used P-element primers along with primers I designed that are complementary to the DNA strand outside of the suspected deletion site. Using genomic DNA from the ED6280 fly, I amplified and sequenced the suspected junctions of the deletion. I aligned the sequencing results with the wild-type genomic fly DNA and was able to deduce the specific junction site of the deletion. In addition to Mes-4, I found that 5 other genes were deleted in the ED6280 fly. My secondary task this summer was to clone the Zinc Finger X-linked, *ZFX,* gene into a plasmid, since the ZFX protein was shown to interact with NSD1 in the Carpenter lab. This clone will be an important tool for future experiments about NSD1-ZFX interactions.

ABSTRACT

A Phase III Randomized Double Blind Placebo Controlled Trial of LUMINENZ-AT™ (CM-AT) in Children With Autism

KRISTINA L. BUTLER   *Rice University*   *Class of 2011*

There is currently no FDA-approved drug designed to treat autism. The sponsor of this study, Curemark, has developed a proprietary digestive enzyme blend based on research that many children with the disorder have gastrointestinal and dietary issues. Additionally, children with autism may have difficulty producing amino acids, which are vital to brain function, due to enzyme deficiencies in their bodies. The purpose of this study is to determine the safety and efficacy of an investigational drug called LUMINENZ-AT™ (CM-AT) in treating behavioral symptoms associated with autism. Children between the ages of 3 and 8 years with a diagnosis of autism were eligible to partake in a screening visit. After an analysis of an initial stool sample and both medical and neurodevelopmental histories, qualifying individuals were randomized and received either placebo or active study drug for twelve weeks. Behavioral changes were measured using parent questionnaires and interviews, behavioral scales, and stool tests. This study is currently being conducted at twelve sites total across the nation, and data collection will likely continue for another year. If CM-AT receives approval by the FDA, it will be unique in that it targets the underlying physiology of the disorder, and not just the symptoms.

ABSTRACT

Initial Experience with Storz C-MAC video-laryngoscope

KATHERINE A. DOWDELL   *Stanford University*   *Class of 2012*

Sponsored by: Carin A. Hagberg, MD

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Video laryngoscope, C-MAC

Video laryngoscopes generate an improved glottis view and are commonly used to manage difficult airways and to rescue failed attempts of direct laryngoscopy. This study was designed to determine if the C-MAC video laryngoscope provides an improved airway view and facilitates an easy intubation. For each patient, an initial look was taken either directly, with the anesthesiology resident looking at the airway, or indirectly, with the anesthesiology resident looking at the image of the airway on the C-MAC screen. Then, a second view was obtained with the alternate method of laryngoscopy followed immediately by intubation. The factors recorded and analyzed were time and ease of laryngoscopy, the airway view (Cormack-Lehane scoring), and time and ease of intubation. In both randomization groups, the times obtained for both laryngoscopy and intubation were slower with the indirect view as compared to the direct view, but the difference was not statistically significant. However, the use of indirect laryngoscopy with the C-MAC did allow for an improved airway view both before and after the use of external manipulation. The only statistically significant finding was that the C-MAC had an increased number of score 1 views with external manipulation when used second for indirect laryngoscopy (22/25 subjects), as compared to using the C-MAC for direct laryngoscopy with external manipulation on the first look (15/25 subjects). Based on these results, the C-MAC video laryngoscope can improve airway view if used indirectly as compared to direct laryngoscopy and potentially allow for an increased success of intubation.

ABSTRACT

Use of Fluorescent Microscopy (FM) to Determine the Patterns of Adherence (PA) of Enteroaggregative and Diffusely Adherent *Escherichia coli* (EAEC, DAEC) to HEp-2 Epithelial Cells Grown in Suspension.

DANIELA GOMEZ   *Sam Houston State University*   *Class of 2011*

Sponsored by: Pablo C. Okhuysen, MD, Division of Infectious Diseases
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: fluorescent microscopy, diarrheagenic *E. coli*, HEp-2 cell, flow cytometry

EAEC and DAEC are common causes of diarrhea in adults and in children worldwide. These pathotypes are defined by distinct PA to HEp-2 epithelial cells grown in static conditions on tissue culture wells and visualized with GEIMSA staining under light microscopy. Interpretation of adherence assays however is time consuming when dealing with numerous specimens and is non-quantitative. The objective of this study was to determine if fluorescent dyes can facilitate the identification of EAEC and DAEC using FM and if staining and PA could be determined in HEp-2 grown in suspension in preparation for quantitative flow cytometry studies. EAEC, DAEC and a non adherent *E. coli* strain (HS) in stationary growth phase were stained with Green cell tracker (GCT) and added to HEp-2 cells grown in suspension and previously stained with Red cell tracer or ethidium bromide (EB). We found that using a combination of GCT and EB, we could visualize the PA characteristic of EAEC and DAEC to HEp-2 cells grown in suspension. In flow cytometry experiments, we noticed that live bacteria had variable proportions of staining, likely reflecting ongoing growth during assays. We conclude that EAEC and DAEC adhere to HEp-2 cells grown in suspension and the PA can be visualized using two fluorescent stains. Future experiments will allow us to identify and quantitate EAEC and DAEC PA by flow cytometry.

ABSTRACT

Adenylyl Cyclase

SUJANA GOTTUMUKKALA   *University of Houston-Downtown*   *Post-bacc*

Sponsored by: Carmen W. Dessauer, PhD, Department of Integrative Biology and Pharmacology

Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: Adenylyl cyclase, G proteins, Gβγ, N-terminus, C1 domain

Adenylyl cyclase (AC) is a G-protein regulated family of enzyme isoforms that synthesize cAMP, the secondary messenger in a number of cell signaling pathways that control important physiological functions including the rate and force of cardiac contraction, learning, and memory. Since many pharmaceuticals modulate cAMP production, it is essential to understand how AC is regulated by G-proteins. Among the AC isoforms, the catalytic domains (C1 and C2) are highly homologous but the N-terminus (NT) is variable with isoform-specific roles. The NT of AC5 (AC5-NT), which consists of 195 amino acids, has been demonstrated to both scaffold inactive G-proteins and interact with the C1 domain. Previous work suggests that the binding sites for both Gβγ and the C1 domain are contained within a 69 amino acid region of AC5-NT (60-129). To further localize the site of Gβγ binding and distinguish between Gβγ and C1 binding sites, various GST-tagged AC5-NT truncations and a QER mutation affecting amino acids 103-105 were expressed in *Escherichia coli*. The proteins were purified by glutathione affinity chromatography. Gβγ and C1 binding was analyzed using GST-pull down assays and antibodies for Gβ and the hexa-histidine tag on C1. Results revealed Gβγ binding in both the 60-129 and 1-60 regions, indicating at least two Gβγ binding sites on AC5-NT. Furthermore, although the QER mutation exhibited Gβγ binding, C1 was unable to bind. Therefore, the 102-105 region may only be essential for C1 binding. However, GST-pull down assays with additional AC5-NT truncations are necessary to further localize Gβγ and C1 binding.

ABSTRACT

Voluntary and Reflexive Orienting in Huntington's Disease

JORDAN W. ING   *Washington University in St. Louis*   *Class of 2013*

Sponsored by: Anne B. Sereno, PhD, Department of Neurobiology and Anatomy
                 Saumil S. Patel, PhD, Department of Neurobiology and Anatomy

Supported by: University of Texas at Houston Medical School – Summer Research Program

Key Words: Huntington's Disease, eye movements, pro-saccade, anti-saccade

Research has shown that individuals with Huntington's Disease (HD) exhibit impaired cognitive abilities and muscle coordination. The purpose of this study was to use eye movement (EM) tests to better understand voluntary and reflexive orienting in HD patients. Eleven healthy volunteers, each of them gender and age matched (within 3 years of patients' age; ave=0.8), were asked to perform visual tasks while an infrared eye tracker recorded their EMs. HD patients were previously tested in the same way. Participants were told to fixate on a central point, which would vanish and reappear in one of four surrounding boxes (directly above and below, to the right and to the left). In the pro-saccade task, the subject was told to make an EM to the box containing the point (reflexive orienting). In the anti-saccade task, the subject was to look at the box opposite the one containing the point (voluntary orienting). Compared to the controls, the HD patients had significantly slower response times and greater error rates in vertical pro-saccade trials (p<.01 for both). Further, their response times were significantly greater for vertical than horizontal pro-saccades (p=.035). This discrepancy in dysfunction suggests degeneration in specific areas of the brainstem where control of vertical and horizontal EMs is physiologically segregated. Additionally, HD patients made greater errors than control subjects in both vertical and horizontal anti-saccade trials, indicating a deficit in basal ganglia-thalamo-cortical processing necessary for voluntary EM control. These behavioral markers not only improve our understanding of the pathophysiology of HD, but also aid in clinical diagnosis and provide behavioral measures to evaluate treatment of the disease and its effects on different brain regions.

ABSTRACT

Renal Cell Carcinoma Bioinformatics

KAREN LEE   University of Texas at Austin   Class of 2011

Sponsored by: Robert J. Amato, DO, Dept. of Internal Medicine, Director Division of Oncology

Supported by: The University of Texas at Houston Medical School, Robert J. Amato

Key Words: Renal Cell Carcinoma

Background: Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults and involves cancer cells in the tubules of the kidney. Neither systemic chemotherapy nor radiation has proven effective for patients with metastatic RCC. Targeted therapies such as sorafenib (Nexavar), sunitinib (Sutent), temsirolimus (Torisel), and everolimus (Afinitor) work by blocking different pathways in cancer cells to stop its proliferation.

Methods: I participated in the RCC bioinformatics program by performing a retrospective chart review of an ongoing patient population. I reviewed baseline clinical information, including details of tumor stage and grade, location of metastatic disease and prior therapies. As patients were seen in clinic, I documented any changes in disease state and treatment plan.

Results: No analysis was performed.

Conclusion: This data set can be utilized in the future for prognostic modeling.

ABSTRACT

Effects of Gamma Radiation on Enzymatic Components of the Nitric Oxide Signaling Pathway

JONATHAN MARQUEZ   *Yale University*   *Class of 2013*

Sponsored by: Iraida G Sharina, PhD, Department of Cardiology
                 Marie-Francoise Doursout, PhD, Department of Anesthesiology

Supported by: The University of Texas at Houston Medical School - Summer Research
                 Program

Key Words: Cardiovascular, Cyclic-GMP, Inflammation, Nitric Oxide, Radiation

The nitric oxide (NO) pathway is crucial in the regulation of cardiovascular functions within an organism. The objective of our studies was to investigate if full body ionizing gamma irradiation alone and in combination with inflammation induced by LPS exposure would negatively affect the NO/cGMP signaling pathway by increasing the oxidative stress. Also, if the use of DF-1, a radio-protectant, would aid in mitigating the effects of oxidative stress produced by our treatments.

7 groups of rats: Control, DF-1 treated, LPS treated, irradiated (20Gy cumulative dose), DF-1 30min before Radiation, Radiation 30 min after DF-1, and Radiation+LPS were used to collect samples from nine different tissues (heart, lung, liver, spleen, kidney, gut, brain, muscle, and skin). Total RNA samples were prepared from collected tissues of lung, kidney, and gut and qRT-PCR ($\Delta\Delta C_T$) analysis was used to determine the levels of inducible Nitric Oxide Synthase (iNOS) gene expression.

We determined that irradiation decreased iNOS expression by a factor of .02 in the lung and increased expression in kidney and gut by factors of 1.57 and 33.80 respectively. When radiation was compounded with inflammatory conditions iNOS was increased in kidney and gut and decreased in lung by factors of 1.90, 1.26 and 3.52 as compared with LPS alone. DF-1 when administered prior to irradiation increased in the lung and decreased in the gut iNOS expression by factors of 1.50 and 1.85 respectively as compared to radiation alone. Post-exposure of administration of DF-1 decreased iNOS expression in the kidney and gut by factors of 1.05 and 5.79 as compared to radiation alone. In conclusion, irradiation affected iNOS expression in all investigated tissues and while DF-1 treatments alleviated radiation effects in gut.

ABSTRACT

Human Papillomavirus Type 17 in a B-RAF Inhibitor Treated Melanoma Patient

SARAH NESTER   *Rice University*   *Class of 2012*

Sponsored by: Stephen K. Tyring, M.D., Ph.D., MBA, Dept. of Dermatology

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: B-RAF, human papillomavirus type 17, actinic keratosis, squamous cell carcinoma

A B-RAF inhibitor treated melanoma patient developed squamous cell carcinoma (SCC) and actinic keratosis (AK) lesions. Occurrence of such lesions has been linked to infection with cutaneous human papillomaviruses (β/γ-HPV), particularly in immunosuppressed patients.

Our aim was to determine if these lesions were associated with cutaneous HPV infection. DNA was isolated from paraffin embedded sections of AK and SCC lesions and the DNA quality was ensured with beta-globin reference PCR assay. Nested consensus primer generated PCR technology designed for detection of cutaneous HPV was then applied to the samples. Agarose gel electrophoresis only yielded a putative HPV PCR fragment in the sample pertaining to the SCC. This fragment was then purified, cloned, and sequenced. A nested consensus PCR using PGMY09/11 and GP5+/6+ primers was performed to verify the negative result of the first PCR for the AK sample and screen for a different range of HPV. This PCR assay also yielded a negative result for HPV in the AK sample. NCBI-BLAST comparison of the obtained sequence information from the SCC sample revealed a single infection with HPV-17.

In the literature, HPV-17, a beta-2-HPV, has been linked with development of SCC in immunosuppressed patients with epidermodysplasia verruciformis (EV). There has yet to be any conclusive experimental evidence confirming the exact pathogenic role of this virus type.

ABSTRACT

Regulation of Neuroepithelioma Transforming Gene 1 (Net1) Activity in Cells

MINHEE PARK   *Rice University*   *Class of 2012*

Sponsored by: Jeffrey A. Frost, PhD, Department of Integrative Biology and Pharmacology
Supported by: Jeffrey A. Frost, PhD, Department of Integrative Biology and Pharmacology
Key Words: Net1 activity, EGF, integrin, endogenous

Ras homolog gene family, member A (RhoA) is known to play a significant role in the development of metastases in breast cancer and other tumors. Neuroepithelioma transforming gene 1 (Net1) is a RhoA-specific guanine nucleotide exchange factor (GEF) that activates RhoA by catalyzing the exchange of GDP for GTP. The objective of this project was to identify extracellular stimuli that activate Net1. Considering the relationship among Net1, RhoA and tumor metastasis, identifying stimuli that activate Net1 will provide a deeper understanding of how metastatic progression occurs in human breast cancer.

To monitor the temporal activation of Net1 in response to upstream signals, an affinity precipitation assay was developed to specifically isolate active Net1 from cells. For this assay, glutathione S-transferase (GST) and GST-RhoA(17A), which is a nucleotide-free mutant of RhoA that binds to GEFs, were expressed in BL21-DE3 *E. coli* and purified using glutathione-agarose beads. Once endogenous Net1 in HeLa cells was checked to be active under normal growth conditions, we tried a number of conditions to identify stimuli that would activate Net1. These included stimulation with epidermal growth factor (EGF), which is known to activate RhoA in Hela cells, and integrin activation, which was shown by our lab previously to correlate with Net1 expression and adverse clinical outcome in breast cancer patients. After exposing to various stimuli, cells were harvested and tested for Net1 activation. Our experiments showed that endogenous Net1 was transiently activated both by exposure to EGF and integrin activation in Hela cells. Neither of these stimuli was previously known to activate Net1. Moreover, our results showed that the GST-RhoA(17A) pull down assay is a useful tool to measure endogenous Net1 activation by extra cellular stimuli.

ABSTRACT

Spaceflight "Bubbles" Used To Differentiate Bone Marrow Stem Cells Into Bone-Forming Cartilage.

MIHIR PATEL   *Texas A&M University*   *Class of 2011*

Sponsored by: Dr. Pauline Jackie Duke, PhD, Department of Orthodontics

Supported by: UT Biotechnology Office, UTDB Startup Funds, The University of Texas at Houston Medical School - Summer Research Program

Key Words: Silastic membrane, bone marrow stem cells, cartilage cells

In a previous experiment, flight hardware and a change in CO_2 exposure were used to differentiate bone marrow stem cells into bone forming cartilage for healing bone defects. In the current study, bone marrow stem cells were grown on the Silastic membrane from the flight hardware without the rest of the unit. Our objective was to differentiate bone marrow stem cells on the membrane, producing a flat piece of cartilage rather than a sphere. Methods: Bone marrow cells from 7-9 day old mice were isolated and expanded in culture. After 2 passages, adherent cells were removed from the plate, suspended in medium and inoculated onto the Silastic membrane. The cultures were placed into the incubator for 2 hours without CO_2 and then changed to 5% CO_2. Cultures were observed daily and ½ the medium was changed every other day. After 3-7 days, the cells were fixed, and then embedded in agarose to allow for sectioning and staining. Results: The cells on the membrane differentiated into cartilage cells, which were shown by Toludine Blue staining to have produced metachromatic matrix. Conclusion: Using these techniques, bone marrow stem cells can be differentiated into cartilage cells in a flat configuration suitable for implantation into a calvarial defect. In future studies, a commercially available Silastic membrane (e.g. Flexcell plates) will be used to produce a larger piece of tissue.

ABSTRACT

Effects of resting state on perceptual skill learning

SNIGDHA PEDDIREDDY   *Duke University*   *Class of 2013*

Previous studies have shown that a short nap immediately following a visual discrimination task leads to subsequent improvement in both behavioral and neural performances in the same task. However, little is known about the processes that occur during rest that lead to the observed improvement. One possibility is a neural phenomenon known as replay, which is defined as a reactivation of the pattern of brain activity evoked during a task. Because replay may strengthen local network functional connectivity modified during the task, we hypothesize that it results in the observed offline improvement. Thus, we predict that the amount of replay during the rest period is positively correlated with improvement in performance in the following task. Recordings were taken from a region of the extrastriate visual cortex (V4) from an awake, behaving rhesus macaque during an image orientation discrimination task and interleaved 20-minute rest periods. The recordings were gathered using 16-contact laminar multielectrodes advanced with a computer-controlled NAN microdrive. The experimental paradigm consists of an initial rest period lasting twenty minutes that is used to record baseline neural activity followed by the image discrimination task during which the monkey differentiates between images of same or different orientation. Then, the monkey undergoes a second rest period of equivalent length in which the amount of replay is measured. Replay is measured by assessing the probability that cells coactivated during the task continue to be reactivated together during the second rest period compared to the first. This will demonstrate modifications in network functional connectivity by the task. After another discrimination task, improvements in behavioral and neural performances from the initial task are assessed using psychophysics curves and differences in neuronal d′ values. The d′ value is used to determine how well neurons are able to discriminate between two stimuli (in this case, two differently oriented images). When data from nine sessions were analyzed and averaged, it was seen that an increased amount of rest and, in turn, replay was in fact positively correlated with task performance. This research could lead to developments in drug treatments or noninvasive therapies that facilitate memory consolidation in patients with conditions that lead to impaired memories, such as Alzheimer's or insomnia.

ABSTRACT

Cryo-Electron Tomography of Pathogenic and Saprophytic *Leptospira* highlights novel features and possible virulence mechanisms

GIANMARCO RADDI   *Rice University*   *Class of 2011*

Sponsored by: Jun Liu, PhD, Department of Pathology and Laboratory Medicine
Supported by: The University of Texas Houston Medical School – Summer Research Program
Key Words: leptospirosis, cryo-electron tomography, flagella, cell envelope, bacterial DNA, chemotaxis receptor array, spirochaete motility

As the primary causative agent of the zoonotic disease Leptospirosis, *Leptospira interrogans* is responsible for more than 50,000 deaths each year, primarily in the developing world. Recently, the genome of *Leptospira interrogans* and the non-pathogenic *Leptospira biflexa* has been sequenced, showing the presence of about 400 genes likely involving unidentified mechanisms of pathogenicity. We used cryo-electron tomography (CET) to compare the native cellular ultrastructure of the two *Leptospira* species to uncover some of the unique biological and pathogenic features of these bacteria. By averaging the 3-D images of 496 flagellar motors and 206 cell tips, we obtained ~3.0 nm resolution models of the rotor and stator structures, and of the "hat", a complex polar periplasmic-space assembly anchored to the cytoplasm of the bacteria. Furthermore, we observed previously unrecognized periplasmic filaments that might be responsible for the characteristic helical morphology of these *Spirochaetes*, as well as the most detailed structure of cell envelope to date, with a total of 9 layers visible between inner membrane, lipoproteins, peptidoglycan layer, and a striking outer membrane, 12.5 ± 0.9 nm in width. We also observed a novel chemotaxis receptor array, blebs and extrusions of the outer membrane and proved the identification of ribosome-excluding areas in the center of the bacteria as DNA. Together, while numerous questions remain unanswered, these results help clarify how *Leptospira interrogans* is able to infect humans, confirm the fundamental role of the complex motility apparatus in pathogenicity, and shed some light on the biology, morphology and lifestyle of this deadly bacterium.

ABSTRACT

Role of β-glucuronidase in probiotics and enterotoxigenic bacteria

YE-KYUNG SONG   *University of Houston*   *Class of 2012*

Sponsored by: Lenard M. Lichtenberger, Ph.D., and Elizabeth J. Dial, Ph.D., Department of Integrative Biology and Pharmacology

Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: β-glucuronidase, NSAIDs, *Escherichia coli, Lactobacillus*

A number of nonsteroidal anti-inflammatory drugs (NSAIDs) cause injury to the small intestinal mucosa, which appears to be in part due to the biliary secretion of the drugs. Evidence is currently conflicting whether it is the glucuronidated or deglucuronidated form of the NSAID that is most damaging to the small intestinal mucosa. When NSAIDs are metabolized in the liver, they are glucuronidated and excreted into the bile, which empties into the intestinal tract. Upon delivery into the intestinal tract, β-glucuronidase deglucuronidates the NSAID metabolites. The claim that deglucuronidated NSAIDs cause more injury than their glucuronidated forms is further supported by numerous observations that more intestinal injury occurs in the distal regions of the gut, where β-glucuronidase possessing bacteria colonize. Additionally, in previous clinical studies, administration of probiotics lowered β-glucuronidase levels in patient's feces. The purpose of this study was to prove the hypothesis that probiotics and non enterotoxigenic bacteria have lower levels of β-glucuronidase than enterotoxigenic bacteria, thus causing less injury. This study compared several probiotic strains of *Lactobacillus*, LT/ST toxin negative *E. coli*, and LT/ST toxin positive *E. coli*, the enterotoxigenic bacteria responsible for traveler's diarrhea. A number of *Lactobacillus* strains, LT/ST toxin negative and positive *E. coli* β-glucuronidase and protein levels were determined by the Bio-Rad β-glucuronidase assay kit and the Lowry protein assay respectively, which allowed for direct comparisons between the β-glucuronidase specific activity of different bacteria, based upon amount of fluorescence activity per µg of protein. The enterotoxigenic *E. coli* had only 250-500 RFU/µg, significantly less β-glucuronidase activity than the probiotics (2000-4000 RFU/µg) and LT/ST toxin negative *E. coli* (1700-2500 RFU/µg). Even when the inherent β-glucuronidase activity of the media is factored in, the unexpected finding that the non-pathogenic bacteria have consistently higher β-glucuronidase activity than the pathogenic strains remains unexplained. These results indicate that the bacteria may behave differently in the lumen of the gut as opposed to in the media and perhaps the MRS media in which the *Lactobacillus* were cultured induced an over-expression of the enzyme. Further investigation of β-glucuronidase of cultured bacteria is ongoing.

ABSTRACT

Semantic Deficits in Anterior Temporal Lobectomy Patients

SAMANTHA L. THOROGOOD   *Rice University*   *Class of 2011*

Sponsored by: Nitin Tandon, MD, Department of Neurosurgery
Supported by: The University of Texas at Houston Medical School – Summer Research Program
Key Words: Temporal lobe epilepsy, anterior temporal lobe, semantic deficit

Evidence for the role of the anterior temporal lobe (ATL) in the representation of semantic knowledge comes from studies of peri-operative electro-cortical stimulation mapping as well as reports of word-finding difficulties from patients with temporal lobe epilepsy (TLE) in the language-dominant hemisphere. At issue is the lack of consistent data demonstrating semantic deficits in AT lobectomy patients in cases of intractable mesial TLE. This study aims to clarify the role of ATL by comparing pre and post-operative performance on tasks of category fluency, semantic association, and both visual and auditory confrontation naming. Of particular interest are the specific roles of the left and right ATL which are thought to differentially encode information across categories of living vs nonliving stimuli. For six patients, performance has been assessed in terms of accurate responses and response latency. Detailed analysis of tip-of-the-tongue states and circumlocutions allowed the distinction between impairment at the semantic level (failure to access conceptual knowledge) and at the lexical level (failure to retrieve the word form). We found that subjects perform less accurately on common object and action naming tasks after resection of the left ATL. Within subjects, average response times consistently increased after resection of the language-dominant ATL. We did not observe significant latencies at either the individual or group level on tests of semantic associative ability. As a group, all TLE patients were significantly less accurate at naming living as compared to non-living stimuli (t(5)=3.26, p=.02). From this small sample of patients, it appears that unilateral ATL resection does not consistently result in semantic impairments beyond the observed oral naming deficits in patients with dominant resections.

ABSTRACT

Construction of shRNA Plasmids for Human VIP Gene Family Members

TSENG, CHUN-CHIA   *University of Texas at Austin*   *Class of 2013*

VCP, a valosin-containing protein, is involved in remarkably diverse biological processes in eukaryotic cells. One of the important functions of VCP is related to post-ubiquitylational regulation of protein degradation through the 26S proteasome. VIP proteins belong to a family of proteins that associate with VCP through their common UBX domains. The specificity of VCP is most likely determined by individual VIP proteins. In order to better understand the biological functions of VIPs, it is necessary to do lost-of-function study through a RNA interference approach. Our research purpose is to construct a panel of shRNA vectors that will be able to sufficiently silence the expression of VIP genes in vivo. To do so, we employ a shRNA system created by Dr. Steve Elledge and Dr. Greg Hannon's laboratories. We have modified the shRNA system to fit well with the Gateway cloning system, so we can easily shuttle the shRNA sequences to various destination vectors, including lentiviral ones. Currently, we have made a panel of shRNA entry plasmids targeting 14 human VIP genes. We will test their knocking down efficiency by co-transfection method. Those validated shRNA entry clones will be transferred to a lentiviral vector to further test their silencing efficiency by lentiviral infection approach.

![UTHealth Medical School — The University of Texas Health Science Center at Houston](logo)

ABSTRACT

Title: Neuronal cell resiliency; does this describe the chronic nature of Parkinson's disease?

*ASHTON K. VIAL*   *University of Texas at Austin*   *Class of 2013*

Sponsored by: Roger J. Bick, MMedEd, MBS, Dept. of Pathology and Laboratory Medicine, Mya C. Schiess MD, Dept. of Neurology

Supported by: University of Texas Medical School at Houston Graduate Students Education Committee and the Kanaly Foundation for Parkinson's Research

Key Words: Parkinson's Disease, inflammation, neurodegeneration

The purpose of this study was to determine cell death rates of diverse cultured human neuronal cells following exposure to short term, high dose lipopolysaccharide (LPS). Previous studies have shown Parkinson's disease associated protein aggregations in cell cultures and illustrated resiliency differences in specific cell types in response to exposure to LPS. In this study cultured human microglia, astrocytes, and dopaminergic neuronal cells were treated with high dose LPS and cells were fixed and probed for the intracellular proteins glial-derived neurotrophic factor (GDNF), a protein intimately involved in cell protection, and alpha-synuclein, a protein that is aggregated in PD. Scans were acquired via fluorescence deconvolution microscopy and 3D image reconstruction was performed. Cell models of stacked images were produced and were used to determine changes in protein content changes in each culture. The results revealed a trend of increased levels of α-synuclein only in the microglia (253±52 v 640±88), while GDNF content appeared to remain constant in each of the cell types. Microglia cultures succumbed to LPS treatments much quicker than both astrocytes and neuronal cells, possibly indicating that the lack of resiliency of these cells results in the ensuing 'exposure' of astrocytes and neuronal cells to toxic compounds such as cytokines, thereby demonstrating a time dependent neurodegeneration.
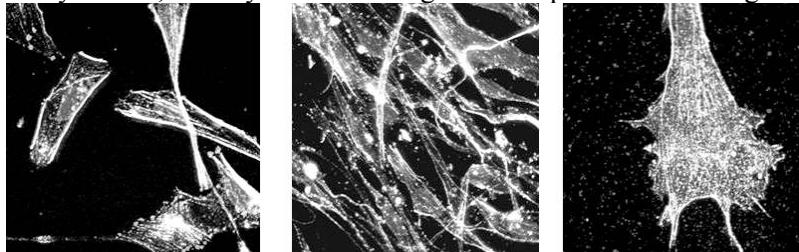
These data agree with determinations made in an LPS treated rat model, in that protein aggregations and the synthesis of protective compounds, such as GDNF, are both time and dose dependent and show that cell culture methods are a reasonable research tool for PD studies.

ABSTRACT

Identification of Mutations in Genes Known to Cause Familial Thoracic Aortic Aneurysms and Dissections

MIRANDA WANG   *Class of 2012*

Rice University

Sponsored by: Dianna Milewicz, MD, PhD, Division of Medical Genetics, Department of Internal Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Aortic aneurysms, TGFBR1, TGFBR2, mutations

Thoracic aortic aneurysms and dissections (TAAD) are the major disease of the aorta, with family aggregation studies indicating up to 20% of patients without genetic syndromes display a familial pattern of inheritance for this disease. Mutations in several genes have been identified to cause familial TAAD, including *TGFBR1*, *TGFBR2, ACTA2*, and *MYH11*. To further investigate mutations in these genes involved in the pathogenesis of familial TAAD, we sequenced 42 affected individuals from unrelated families for the coding region of *ACTA2* and 137 individuals from unrelated families for the kinase domains of *TGFBR1* and *TGFBR2* using intron-based exon primers. We identified two known mutations and one novel nonsynonymous alteration in *TGFBR1*. The novel alteration, F234V, was located in a highly conserved protein sequence and the alteration was predicted to be probably damaging with PolyPhen prediction software. Three novel non-synonymous alterations identified in *TGFBR2,* N234I, V376M, and Y448H, were located at highly conserved protein sequences. The alteration N234I was predicted to be probably damaging, while the other two alterations were predicted to have a benign influence. No mutations were found for *ACTA2*. These results suggest that mutations in *TGFBR1* and *TGFBR2* may have a more significant contribution to the pathogenesis of familial TAAD than previously estimated.

ABSTRACT

Classification of 23 autoimmune and other diseases through hierarchical clustering according to gene associations.

TOM Y. XIA   *Rice University*   *Class of 2013*

Sponsored by: Xiaodong Zhou, PhD, Department of Internal Medicine
Supported by: University of Texas at Houston Medical School – Summer Research Program
Key Words: Autoimmune, GWAS, association, classification

We aimed to analyze the genetic relationship between different diseases through quantity of shared susceptibility genes. We performed a pubMed search for genetic association studies of human complex diseases. After collecting data on genes associated with our 23 diseases of interest from over 800 articles from 2001 to the present, we found 41 genes associated with two or more of our diseases. Hierarchical clustering was then implemented using associations with these 41 genes to classify the diseases into three distinct groups: class I included immune-inflammatory diseases, class II included cardiovascular related problems, and class III for neurological and other diseases. Class I includes HCC, SLE, RA, SSc, APS, pSS, MS, T1D, OA, AS, PBc, HCV, P, and CD, class II includes T2D, IS, CVD, IA, and AA, and class III includes AD, MDD, EH, and NAFLD. Many of the diseases in class I are associated with genes that participate in the Jak-STAT signaling pathway, including IL23R, IL10, STAT4, and PTPN22, suggesting a connection between this pathway and autoimmune disorders. Also, the systemic autoimmune diseases, including MS, pSS, APS, SSc, RA, and SLE, are all associated with IRF5, which plays a role in the Toll-like receptor signaling pathway. SLE and RA are expectedly the most related of all diseases, sharing 12 gene associations. SSc is discovered to be closely related to this group, sharing seven associations with both SLE and RA and an additional association in BLK with SLE only. In addition to being shared within classes, some genes are also shared by different classes, such as TNF alpha, IL6, and CTLA4, which may suggest potential biological events shared in these human complex diseases. This study serves as an example for future disease-association studies, and it can be applied to more than just autoimmune diseases. As more hypothesis-driven association studies and GWAS are completed, we encourage similar studies to be performed to better understand the connection between multiple diseases.

ABSTRACT

Combinatorial Effects of Gamma Irradiation and LPS Exposure on Nitric Oxide Signaling Pathway

WEN ZHU XU   *Rice University*   *Class of 2012*

Sponsored by: Marie-Francoise Doursout, MD, Department of Anesthesiology
Iraida Sharina, PhD, Department of Internal Medicine/Cardiology

Supported by: The University of Texas at Houston Medical School – Summer Research
Program

Key Words: Nitric oxide, cGMP, cardiovascular, radiation, inflammation

The nitric oxide and cyclic GMP (NO/cGMP) signaling pathway plays an important role in vasodilation. Exposure to radiation and inflammatory response increase oxidative stress by increasing the production of free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS). Our objective was to investigate the effect of radiation exposure and inflammatory response separately and together on the enzymatic components of NO/cGMP signaling pathway in vascular bed-rich tissues in normal rat model. We also evaluated the use of DF-1 as a scavenger to protect against oxidative stress.

The study was conducted in 7 different treatment groups, 5 individual animals per group. Rats were exposed to whole body γ-radiation in cumulative dose of 20 Gy. Inflammatory response was induced by injection of LPS (2.0 mL/kg) 30 min after irradiation. Treatment groups included controls (non-irradiated, DF-1 treated, LPS treated) and combination of individual treatments (irradiated, DF-1 treated 30 minutes prior to irradiation, DF-1 treated 30 minutes post-irradiation, LPS treated 30 minutes post-radiation). Tissue samples (brain, skin, heart, lung, kidney, spleen, gut, liver, and muscle) and blood were collected 3 hours after irradiation. RNA was purified from tissues samples and analyzed for expressions of iNOS, eNOS, nNOS sGC (α1, β1), and PKG using qRT-PCR.

QPCR analysis revealed that radiation reduced iNOS expression in lung ($\Delta\Delta C_t$ = -5.43) and increased in kidney ($\Delta\Delta C_t$ = 0.65) and gut ($\Delta\Delta C_t$ = 5.08). As expected, LPS increased iNOS expression in lung ($\Delta\Delta C_t$ = 3.51), kidney ($\Delta\Delta C_t$ = 8.09), and gut ($\Delta\Delta C_t$ = 8.60). Radiation in combination with LPS increased expression in lung ($\Delta\Delta C_t$ = 1.69), kidney ($\Delta\Delta C_t$ = 9.01), and gut ($\Delta\Delta C_t$ = 8.93) DF-1 reduced expression in lung ($\Delta\Delta C_t$ = -6.41), kidney ($\Delta\Delta C_t$ = -0.76), and gut ($\Delta\Delta C_t$ = -0.32). DF-1 did not seem to protect against effect of radiation in lung ($\Delta\Delta C_t$ = -5.18 prior to exposure and $\Delta\Delta C_t$ = -5.63 after and kidney ($\Delta\Delta C_t$ = 0.65 prior to exposure and $\Delta\Delta C_t$ = 0.59 after), but did have protective effect in gut ($\Delta\Delta C_t$ = 4.19 prior to exposure and $\Delta\Delta C_t$ = 2.55 after).

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ABSTRACT

Mutational Analysis of *PHEX*, *FGF23*, *DMP1* in 3 Subjects with Renal Phosphate Wasting Disease

YOKO AKAIKE   *University of Tokushima*   *Class of 2012*

Sponsored by: Mary D. Ruppe, MD, Department of Internal Medicine, Endocrinology, Diabetes and Metabolism Faculty

Key Words: XLH, ADHR, ARHR, *PHEX*, *FGF23*, *DMP1*

X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR) and autosomal recessive hypophosphatemic rickets (ARHR) are genetic forms of rickets that cause lower extremity deformities, bone pain, short stature and dental abnormalities. These types of rickets are related to mutations in *PHEX*, *FGF23*, *DMP1*, respectively. We analyzed mutations of these genes in 3 subjects with renal phosphate wasting disease as part of a larger project that assesses the frequency of mutations in the genes known to cause these types of disorders. Genomic DNA was isolated. PCR amplification of genomic of all exons and the flanking intronic regions was performed with direct sequencing via ABI 3100 automatic sequencer following standard protocol for BigDye™ terminator sequencing. The resulting sequence was analyzed utilizing NCBI Blast, ClustalW and CodonCode Aligner. To assess the effect on protein in function of any missense mutations, SIFT and PolyPhen analysis was carried out. A damaging *PHEX* mutation (1936G>A; 646D>N) that has not previously been described was found in subject 231. There was a heterozygous variant in *FGF23* exon3 in subject 229 (716C>T; 239T>M).There were heterozygous variants in *DMP1* exon6 in subject 229 (205A>T; 69S>C) and subject 234 (1218C>T; 406S>S). In conclusion, a novel *PHEX* mutation was detected in one subject while the genetic abnormality in the other two subjects was not identified. This suggests that genes outside of the ones that have been described are yet to be discovered. The information gained by this work will help to define the genetic variability that occurs in phosphate wasting rickets. This will improve our ability to diagnosis and treat these rare conditions.

ABSTRACT

Reduced TNF-α and IFN-γ mRNA in lungs of mice correlates with protective pathology in MTB infected mice immunized with the BCG vaccine formulated with lactoferrin adjuvant

YA-WEN CHIANG   *China Medical University*   *Class of 2013*

Introduction: Lactoferrin, an iron binding protein found primarily in mucosal secretions and granules of neutrophils, possesses immune modulatory properties that include enhancement of the delayed type hypersensitivity against BCG antigens. Previous studies demonstrate that bovine lactoferrin added to the BCG vaccine enhanced host protection after challenge with virulent Erdman *Mycobacterium tuberculosis* (MTB), as observed by comparable decreases in organ CFU, reduced granuloma lesions, and increased antigen specific IFN- production. In this study, BALB/c and C57BL/6 mice were examined for levels of TNF-α and IFN-γ mRNA in tissues post infection with virulent MTB, vaccinated with or without BCG and lactoferrin.

Methods: BALB/c or C57BL/6 mice were immunized and boosted at 8 weeks with BCG, or with BCG and bovine lactoferrin (100 μg/mouse). One group remained non-immunized. At 12 weeks post-vaccination, mice were aerosol challenged with Erdman MTB and monitored through 150 days post-challenge. Message levels were quantitated by gel analysis of RT-PCR products using NIH Image software, converted to Relative Value Units (RVU) and normalized to beta actin expression.

Results: Levels of message varied greatly between mice. However, mice immunized with BCG in the presence of bovine lactoferrin demonstrated decreased mRNA for TNF-α (eg. 169.9 RVU) compared to non-immunized control mice (213.4 RVU), at 65 days post infection. Levels for IFN- were elevated (187.4 RVU) compared to non-immunized mice (162.0) and BCG immunized controls (165.0 RVU). This correlated with decreased pulmonary pathology and manifestation of disease, and previously found higher T cell IFN- response.
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ABSTRACT

Effect of Indomethacin on Bone Ingrowth into a Porous-metal Implant

TAO. HE   *Shanghai Jiao Tong University*   *Class of 2012*

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

Key Words: Indomethacin, bone ingrowth, micro-CT

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as post-surgical analgesics. Recent studies suggested that their effect on preventing bone healing post-operatively was dosage dependent. Our aim was to find a safe dosage of indomethacin to relieve pain post-operatively without impairing the bone growth. The effect of postoperative administration of both indomethacin and pc-indomethacin (indomethacin with the addition of soy phosphatidylcholine) on bone growth into porous titanium implants was evaluated in a rat model. Porous titanium pins were placed into the medulla of the rat's femur through the knee of the animal. 100 animals were divided equally into 5 groups. One group of animals did not receive any treatment and acted as controls. The other four groups received either indomethacin or pc-indomethacin (2mg/kg/day). In the animals receiving one of the two NSAIDs, two different dosing regimes were tested. One group only received injections for the first 2 days after surgery with no additional NSAID dosing; the other group received injections for the first 2 days and followed by oral dosing until sacrifice. The animals were euthanized at the 14th day or 28th day postoperatively and the femurs receiving surgery were harvested. Both micro-CT scans and quantitative histologic analysis were performed to quantify the bone ingrowth into the implant. Previous studies showed that no influence was observed at the dose of 1mg/kg/day. And at the dose of 2mg/kg/day, the postoperative pain was effectively relieved. At this time, analysis is ongoing. We expect to see that using indomethacin at a dose of 2mg/kg/day is safe for the adult rat acting as analgesics without any influence on bone healing. Since the addition of soy phosphatidylcholine promotes the ability of indomethacin to cross lipophillic membranes of a target cell to exert their intended actions, we hope to find a more potent effect of these drugs on relieving pain.

ABSTRACT

Exogenous Nucleotides Effect on Gut Ischemia-Reperfusion Injury

WENJIN WU   *Shanghai Jiaotong University School of Medicine   Class of 2013*

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

Key Words: nucleotides, ischemia-reperfusion injury, intestine

Purpose: Dietary nucleotides have been proven to play an important role in normal immune response and wound healing. They are also necessary for recovery from intestinal irradiation injury, and to facilitate normal enterocyte maturation. The purpose of our study is to establish a mouse model of intestinal ischemia-reperfusion injury and to explore whether an RNA supplement is required for the salutary effect following intestinal injury.

Materials and methods: C57BL/6 mice were fed for 2 weeks in three diet groups, including chow control, nucleotide free (NF) diet and NF + 0.25% w/w RNA (NFR) diet. Groups were divided further into two treatment groups: Sham with laparotomy only and SMAO with superior mesenteric artery occlusion (SMAO) for 45 minutes and 30 minutes reperfusion. Ileum and jejunum tissues were collected and assessed for tissue wet and dry ratio to measure tissue edema. Additional evaluations will be performed for histology analysis, total protein, and molecular mechanisms with additional number of mice.

Results: There was no significant difference in average body weight between different diet groups and surgery groups. For all the three diet groups, wet and dry tissue ratio was higher in SMAO group than in Sham group. However, the differences were not significant in mice with NF and NFR diet (p>0.05) (4mice per group).

Conclusion: We successfully established mouse gut ischemia-reperfusion model through 45 minutes of SMAO and 30 minute reperfusion. The existing pilot data might not suggest the effect of exogenous nucleotides on relieving the tissue edema in gut injury. We also need more histological evidence and data to confirm our hypothesis.

ABSTRACT

Insulin Resistance is Cardioprotective-A totally new concept

YU-LUN, CHOU   *China Medical University*   *Class of 2015*

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

Key Words: insulin resistance, hyperglycemia, heart, apoptosis

Hyperglycemia is a risk factor for premature death and disability from heart disease. Although the metabolic dysregulation of diabetes mellitus has been associated with impaired cardiac function, we speculate that insulin resistance may protect the heart from fuel toxicity when substrate supply exceeds the heart's energy needs. We tested this hypothesis in a rat model of insulin resistance induced by feeding Sprague Dawley rats a high-sucrose diet. An insulin tolerance test confirmed that the animals develop insulin resistance after 5 to 8 weeks on diet. Hearts were isolated and perfused in high glucose conditions. Rates of cardiac glucose uptake were lower in hearts from sucrose-fed rats than in controls. Unexpectedly, rates of glucose oxidation were increased compared to control rats. Because lactate release into the buffer remained unchanged, we speculate that high glucose supply leads to accumulation of glucose intermediates in the heart of control rats. We next incubated H9c2 cardiomyoblasts rendered either insulin resistant (chronic high glucose treatment) or insulin sensitive (by troglitozone treatment) in a hyperglycemic medium for 5 hours. Compared to untreated cells, glucose uptake was reduced in insulin-resistant cells, while glucose uptake was enhanced in cells treated with the drug. Interestingly, the rate of glucose uptake was positively correlated to cell death, as measured by caspase3 activity. The results suggest that insulin resistance limits the intracellular accumulation of glucose intermediates in the heart, and reduces hyperglycemia-induced cell death.